HYPERTENSION

VOLUME VI

MINERAL METABOLISM

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INTRODUCTION

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The subject of this year s conference makes me think of Rachel L Carson s best seller The Sea Around Us perhaps our theme might be called Hypertension or the Sea Within Us

I hope now to bring us all up to the same starting point at the water s edge so we can swim together As you know you and I are about sixty percent water Into this medium the good Lord dumped a little more than one pound of salt *That pound according to some authorities is a mighty busy one It* races around so that well over fifty pounds cross the walls of our blood vessels in one direction or another in the course of a day About three pounds are filtered through the glomeruli of our kidneys daily — all but a tea poonful is reabsorbed Plus or minus one or two teaspoons in via the diet and one out via the urine and we remain in balance with mechani ms available to handle a variety of conditions — from low salt diets to Smorga bord from the Sahara to an overdose of cascara

The hypertension story is as follows Based on the theory that there may be chloride retention in hypertension Ambard and Beaujard in 1904 reported that the blood pressure fell after salt poor diet Pfeiffer in 1911 shifted the emphasis to odium rather than chloride Allen and Kempner have been among the enthusiastic supporters of low odium diets in hypertension Today after considerable controversy and a voluminous literature it is accepted generally that rigid sodium restriction will often lower the blood pressure and that this is achieved directly on the peripheral re istance through the modification of a non neurogenic component Most of us would agree that some patients have fewer ymptoms congestive failure is helped and retinopathy is improved We debate about the heart size after salt restriction feeling that only the failing heart gets smaller We are troubled about the limitations and restrictions impo ed on the patient not only becau e of the unpleasant features and the unpalability of such diets but also becau e they do not eem to help the kidneys very much in fact if we re trict the salt too much in the pre ence of renal damage the kidneys may lo e too much alt with resultant symptom and further impairment of renal function The

benefits of the low salt diets on blood pressure are less evident in patients with the accelerated form of hypertension.

Let us briefly summarize a few of the results which have been reported on the experimental side. In many forms of experimental hypertension the addition of sodium chloride seems to make the hypertension worse and the pathological changes more advanced. We are under the impression that the hypertensive patient tolerates a low sodium diet somewhat better than a normotensive subject if there is no renal damage present, and that other differences in response are present, such as a somewhat greater sodium diuresis when hypertensive individuals are treated with thiocyanates. There are reports of an increase in sodium in the vascular musculature of hypertensive animals, of increases in total exchangeable sodium, and of an abnormal distribution of tissue electrolytes in hypertensive subjects. Desoxycorticosterone requires at least some dietary salt for its pressor action. Finally, several groups have reported that there is an augmentation and perhaps an increased rate of excretion of a sodium load when given to hypertensive subjects in comparison to control studies in normotensive individuals.

There are also some puzzles. For example, low sodium diets reduce the blood pressure but also stimulate the elaboration of aldosterone; why no rise in blood pressure? Desoxycorticosterone in the presence of sodium elevates the blood pressure and lowers the total amount of potassium in the body, but there are several reports that a low potassium diet may lower the blood pressure. The rauwolfia alkaloids lower the blood pressure yet on occasion cause sodium retention. Why no elevation of blood pressure in these cases?

Before closing I should like to mention a few of the reasons for caution in the way we conduct our studies. Many reports in the literature dealing with sodium restriction or load fail to consider the antecedent diet of the patient. For example, it takes on the average at least four days after a change in diet to achieve electrolyte balance; therefore an adequate baseline is essential. Furthermore, there are big differences in patients who have a little renal damage as compared to those with no renal damage. One must be certain that renal responses do not reflect damaged kidneys rather than disturbed metabolism.

The weight of evidence today favors an association between sodium and the blood pressure. There are many reports now that lend support to the idea that there is a disturbance in sodium metabolism in hypertension. What is cause and what is effect remains to be seen; whether sodium is related to a fundamental mechanism is still in doubt. I feel sure that some of the speakers in this symposium will bring us much closer to the truth about the sea within us and perhaps in this way we will be a little less at sea.

SODIUM AND HYPERTENSION

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A RELATION between the blood pressure level and the amount of salt ingested has long been suggested by the hypotensive effects of low salt diets in some cases of hypertension (1) and in pre eclampsia (2) as well as by the clinical value of a high salt intake in the control of the hypotension of adrenal insufficiency (3) A high salt intake can produce rises in blood pressure in a variety of experimental animals similar mechanisms may be operative in the production of essential hypertension in man

A stimulus to the following epidemiologic study was the apparently high incidence of hypertension among Negroes The impression that this race was particularly subject to hypertension had already been suggested by several statistical studies from the South (4 6) from prison populations (7) and from the tropics (8 9) Etiologic factors such as diseases of the kidney the adrenal gland or the nervous system have not clarified the mechanisms of hypertension in these cases Environmental factors such as previous history and occupation usually provide no significant clues Recently a survey of the hypertension produced in animals by a high salt diet impelled us to re examine the possible relation between salt intake and blood pressure level

A further stimulus to this study came from the report of Dahl and Love (10) who asked employees of the Brookhaven National Laboratory whether they salted their food before tasting after tasting or rarely Their results showed that patients with blood pressures above 140/90 had a greater tendency to salt their food before tasting while hypertension was infrequent in individuals who rarely salted their food

Salt Ingestion in Man

In this cooperative study with Dr Milton Terris of the Department of Public Health and with Dr Franklin Zeplowitz a questionnaire was designed to obtain information on the salt ingestion habits of patients in the associated teaching hospitals of the University of Buffalo School of Medicine The study was broadened to include Whites as well as Negroes and a total of 210 patients was studied

The medical records of hospitalized hypertensive patients were examined by a medical student for comparison a normotensive on the same ward

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who was matched as far as possible for age ex height weight race and occupation was also selected These data along with the diagnosis the duration of the stay in the hospital and blood pressures on admission while in the hospital and at the time of the questionnaire were placed on a special form The names of the matched pairs without other identifying data were then given to a second student who used a second questionnaire to obtain information on previous habits of diet salt and water intake

Analysis of the data obtained showed that the following factors did not correlate with the blood pre sure previous residence in the South amount of salt used in cooking whether the patient salted his beer or watermelon the volume of fluid taken and the degree of nocturia Blood pressures of the patients correlated poorly with the cause of death of parents although more than twice as many hypertensives as normotensives reported a stroke in their parents

Out of the 240 record obtained many were eliminated becau e of acute alcoholism (which usually gave ri e to transiently elevated blood pressure levels on admission) a tay in the hospital of more than one month primary renal disease and previous treatment of hypertension as well as for unmatched case The remainder of the data could be matched satisfactorily for 126 patient The e records were then divided into four categories according to the diastolic pre sure at the time of the interview below 80 mm Hg in the 80 s in the 90 s and above 100 mm Hg Three ets of correlations then appeared

Only marginal support for the pecific findings of Dahl and Love (10) appeared in the answers to que tions concerning the salting of food prior to tasting Thus twenty five percent of the patients with diastolic pressure below 80 mm Hg salted their food before tasting thirty percent in the group with pressures in the 80 s forty five percent with pressures in the 90 s and forty percent in patients with diastolic pressures of 100 mm Hg or more (Fig 1) Our data therefore suggest that the simple salting of food at the table prior to ta ting is not a sufficiently satisfactory sign of the presence of a rai ed blood pre sure

A better correlation was found between the blood pressure level and the respon e to a question concerning the amount of salt used at the table (Fig 2) Thu eventy percent of the group with pres ures below ninety stated that they used either *little* or *no* salt at the table while eventy percent of the patients with pressures of ninety mm Hg or more stated they used *some* or *much* salt at the table

It is immediately apparent that the e qualitative terms are eriously limited ince what may seem to be *much* for one patient might be *little* for another Neverthele s it was of interest that o many hypertensives eemed to think that they u ed considerable salt at the table while normoten ives generally had a contrary impre sion

FIGURE 1 Percentage of appro imately thirty pat ents in each of four diastol c blood pressure levels who reported that they u ually salted their food b fore ta tin

FIGURE ? Percent ge of pproximately thi ty patients in each of four diastolic blood pres ure levels who repo ted th t they used some or much" salt t the table

Support for the thesis of a higher salt intake in hypertension was found in an analysis of questions concerning the intake of highly salted foods A significant correlation was shown between the blood pressure level and the number of highly salted foods which each patient reported he ate regularly (Fig 3) A list of fifty highly salted foods was read to each patient and he

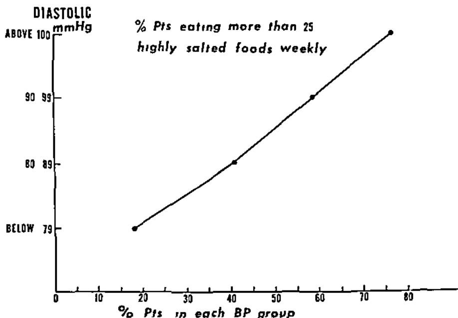


FIGURE 3 Percentage of approximately thirty patients in each of four diastolic blood pressure levels who reported that they ate more than twenty five highly salted foods at weekly intervals

was asked if he took each of these daily weekly monthly or rarely The e foods included salt or smoked fish herring cod clams crab meat flounder oyster fresh or canned salmon tuna and sardines among the meats listed were corned chipped or dried beef canned chicken smoked meats ham salt pork bologna salami liver sausages and frankfurters *vegetables* included sauerkraut canned corn a paragus mushrooms or tomato juice olives beans chili canned soups salad dressings and mayonnai e alted snacks included french fried or chipped potatoes pretzels salted soda crackers chee es nuts and dairy products including buttermilk salted butter or margarine

Only twenty percent of the patients with blood pre sures le s than eighty mm Hg ate twenty five or more of the e alted foods at approximately weekly intervals forty percent of the patients with dia tolic pressures in the 80 s and fifty five percent of tho e with pre ures in the 90 s reported more than

twenty five such foods being taken while seventy five percent of the patients with pressures of 100 mm Hg or more reported this higher intake of salted foods

The data presented above suggests that hypertensive patients may have a greater than normal appetite for salty foods A possible relation between salt intake and hypertension has recently been emphasized by Moser (11) who reports that hypertension is so common in the Bahamas that almost everyone on these islands has a relative with the high blood or has had a stroke or has died of hypertension In some of these islands the drinking water is said to contain a high concentration of sodium chloride A clinical impression is that half of the West Indians over age of forty actually have systolic hypertension by commonly accepted criteria More than twenty percent of the males and thirty percent of the females in the third decade of life had diastolic pressures over 100 If ninety mm Hg were accepted as a criterion for diastolic hypertension two thirds of the islanders over forty would be in this classification

A remarkable finding in the Bahamas is the high salt intake on some of the islands (11) As a baseline we may consider that the water supply in Nassau and some of the outer islands is said to contain three grams of sodium chloride per liter in Eleuthera one of the smaller islands it is five grams per liter If some of these natives consumed two liters of water a day they would be getting ten grams of sodium in their daily water ration alone The Bahamans are reported to drink a great deal of water because of a constant thirst possibly induced by the hot climate as well as by a high salt intake Further a common item of the diet is salt pork which contains about eight grams of salt per pound

While the relation of salt intake to hypertension is only now under intensive clinical investigation a considerable literature on such a relation in animals has appeared in the last decade

Salt induced Hypertension

Hypertonic salt solutions as drinking water have been demonstrated to raise blood pressure in various experimental animal Some years ago we showed that the addition of table salt to the drinking water of the chick produced a rise in blood pressure within a few days (12) Thus 0 9 percent sodium chloride in the drinking water produced a pressure rise (optical recording) from an average of 135/125 mm Hg to an average of 155 135 mm Hg in two weeks When the concentration of salt was increased to 1 2 percent the blood pressure increased further to 180/150 mm Hg Within a week after normal tap water was provided the pressure fell sharply to the control level When the animals were again placed on drinking water containing 1.2 percent salt the blood pressure rose again falling toward normal at a somewhat slower rate when the animals were once again permitted to drink tap water The ratio of wet heart weight to body weight

the animal might properly be considered to be hypertensive compared with its own basal level It is probable that similar problems of differentiation of normotensives with pressures in the upper range of their distribution from hypertensives in the lower range of their distribution are also

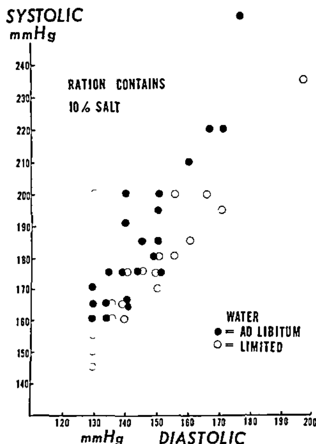


FIGURE 5 A plot of systolic vs diastolic arterial pres ures in chicks at f fteen weeks of age All animal had salt added to their mash The sol d dots represent values for chicks taking tap water ad libitum The open circles represent values for animals receiving l mited drinking water

pre ent in man This would suggest that the measurement of the blood pres sure alone may not be sufficient to determine the pre ence of a hyperten ive proce s in a given individual

The reduced pul e pressure of the animals on the alt diet may be related to changes in aortic tone or to a reduction in stroke output The e mechani ms

have not yet been analyzed in our laboratory. The change in pressure is probably not associated with change in body fluid compartment. While a transient edema appeared shortly after the onset of a high salt intake, the weight fell in short term experiments at the end of the first week on salt and it was assumed that dehydration had probably taken place. This suggested that one of the contributing mechanisms may be the relative amounts of salt ingested compared to the water available for its excretion.

Water Intake Experiments

To test the role of water intake in salt fed animals, experiments were carried out in sixty chicks given mash to which table salt was added. In the second week of life one percent sodium chloride was mixed with the mash; this was increased to three percent during the period three to six weeks, to five percent during the sixth week, to six percent during the seventh week, and to ten percent during the last eight weeks of the experiment.

Unlimited drinking water. Half the animals were allowed fresh tap water ad libitum. The feed intake per kilogram of body weight was approximately equal to that of animals on a normal mash diet without salt. These animals gained weight at a normal rate and showed no signs of toxicity. Twenty-four of the thirty animals survived to the end of the study. The blood pressures in these animals averaged 185/145 with a mean of 160 mm Hg (Fig 5) and a heart rate of 330 beats per minute.

Analysis of the data showed that some of the animals had diastolic pressures below 130 mm Hg, or distinctly within the normal range. Nine of the twenty two chicks studied had diastolic values of 150 mm Hg or higher.

Limited drinking water. Another group of thirty chicks was given the same salted diet except that these animals were provided with only ten percent of the water taken by the first group. These animals showed toxicity and a large number of them died during the course of the experiment. The animals grew poorly, weighing only half their control. The heart rate of some of them was as slow as 250 beats per minute, but the slowed rate was unrelated to changes in pressure or in pulse pressure. At the end of the experiment the blood pressures in this limited water group were essentially similar to the comparable group which had access to unlimited drinking water (Fig 5).

Comparison of the results obtained with the preceding two groups shows that the development of toxicity as indicated by poor growth can result from a high salt intake. However, the availability of an adequate supply of drinking water reduces this manifestation of toxicity. By contrast the hypertensive effects of a high salt intake seem to persist whether or not such toxicity is present. Furthermore, the hypertension induced by a high salt intake appears unaffected by the availability or restriction of fresh drinking water.

Animals taking salt in the drinking water took more salt and had generally higher pressures than did those taking salt mixed with the mash.

This may suggest that the hypertensive process is a function of the total quantity of sodium ingested. The animals taking the most salt also had larger adrenal glands per kilogram of body weight (Table 1). In man with essential or renal hypertension the adrenals are also reported to increase about twenty five percent in weight (13).

TABLE 1

EFFECT OF SALT ON BODY AND ADRENAL WEIGHTS IN CHICKS

	Number of *animals*	Average *Weight* kg	*Adrenal Wt* / *Body Wt* x 10^4	Salt added *g/kg/* day
Water	39	1.7	9	0
Saline	13	0.9	14	9
Water ad lib	21	1.7	9	5
10% Salt in ration				
Limited Water	18	0.9	10	5

(See text for details of experiment)

Self Selection Experiment

Excess salt intake disturbs water balance and polydipsia and polyuria develop. Disturbances of the electrolyte pattern brought about by salt or desoxycorticosterone administration show that these changes depended on renal function. We have examined the role of the kidney in the mechanism of polydipsia and salt hunger (14). Rats were placed in Richter self selection cages (15) each with four graduated tubes containing either tap water or solutions of five percent glucose, 0.9 percent sodium chloride or 0.9 per cent potassium chloride. The control animals preferentially took a daily average of eighty ml glucose solution and six ml of saline. The administration of desoxycorticosterone caused the animals to increase their saline intake to eighty ml of saline in addition to the usual glucose intake. On the first day after total nephrectomy the animals sharply reduced the saline intake to eleven ml although an average of thirty two ml of glucose solution was taken. A small amount (ten ml) of glucose solution was taken on the second day but saline was avoided. No fluids were taken on the third and fourth day after nephrectomy.

These results indicate that the increased sodium appetite induced by desoxycorticosterone is dependent on a continuing diuresis. It may be considered that the administration of DCA raises the ability of the cells of the

body to hold sodium and in this way causes a relative salt deficiency or hunger The taking of sodium by mouth then causes considerable spillage which must be replaced When the loss is stopped as after bilateral nephrectomy sodium appetite ceases The role of these sodium exchange mechanisms in the development of hypertension remains to be determined

DISCUSSION

A number of workers hold that arterial hypertension is secondary to a disturbance in the salt water balance in the body Eichelberger (16) has shown that the sodium chloride content of skeletal muscle increases in renal hypertensive dogs while the potassium decreases and the extracellular water tends to increase Green and Sapirstein (17) have noted that in hypertensive rats in which only a portion of one kidney remains intact the total body body sodium increases as much as twenty five percent Since the plasma sodium remains at normal level and the extracellular space is not markedly expanded some of the retained sodium probably enters the intracellular compartment Braun Menendez (18) holds that an increase and maldistribution of sodium and water occurs in the three types of hypertension induced by disturbing the renal blood flow by removing both kidneys or by administering desoxycorticosterone

Hollander and Judson (19) have shown that hypertensive patients have an increased ability to excrete sodium perhaps associated with an increase in intracellular sodium They also suggest that the distribution of sodium rather than its total in the body might be related etiologically to the raised blood pressure Muirhead *et al* (20) have reported that the administration of pressor drugs produces a rapid measurable fall in the plasma sodium with a concomitant rise in potassium they believe these changes reflect the entrance of sodium into the cellular compartment as potassium leaves the cell These effects are reversed at the end of the pressor infusion Similar ionic changes in the plasma have been observed by the Friedmans (21)

Tobian and Binion (22) have reported that water and sodium accumulate in muscle brain and in the blood vessel wall of hypertensive animals and they have suggested that the increased peripheral resistance may result from edema of the vessel wall Such edema could act to reduce the lumen of the arterioles From physical considerations even a small reduction in the radius of a blood vessel would markedly reduce the blood flow through it (Poiseuille) unless a higher pressure were provided

The blood pressure will fall if sufficient sodium is lost from the body as occurs in rigid dietary sodium restriction in man For many years [illegible] effect could not be produced in the dog since the sodium con[illegible] tion of this animal is so efficient that sodium loss is minimal even under [illegible] ditions of rigid restriction (23) The sodium blood pressure relatio[illegible]

even in this species however since intensive peritoneal lavage can reduce the plasma sodium from about 145 to 115 meq per liter with a reduction of the blood pressure to normal in hypertensive dogs Normotensive dogs subjected to the same procedure have no fall in pressure (24)

Sodium restriction also reduces the blood pressure of hypertensive rat and increases their survival time (25) Somehow these animals seem to appreciate this physiological situation since they will decrease their sodium intake when a choice of drinking solutions is permitted This low salt preference of hypertensive rats is maintained even after adrenalectomy during administration of desoxycorticosterone or during a forced increased fluid intake (26) On the basis of more complex experiments using the parabiotic rat Ledingham has shown that the hypertension which develops in a nephrectomized parabiont is followed by a return of the blood pressure to normal upon removal of the adrenals of the hypertensive animal Ledingham (27) thus feels that the raised blood pressure is due to an adrenal pressor material normally eliminated or neutralized by the kidney In previous studies we have shown that the pressor principle of Goldblatt hypertension is eliminated by a similar mechanism that is by the metabolic activity of normal kidney tissue (28)

A factor which probably contributes to the difficulty in determining a quantitative relation between sodium intake and the blood pressure level is the complexity of sodium potassium balance Thus a high sodium intake can lead to a period of arterial hypertension but this may be followed by the development of severe hypokalemia generalized weakness and a fall in blood pressure to normal or even subnormal levels (29 31) The reactivity of the arterioles appears to be involved since the pressor responses to epinephrine norepinephrine renin and angiotonin are diminished (32) The mechanism appears to depend on the hypokalemia since administration of potassium salts to such animals causes a return of vascular reactivity to pressor drugs within an hour or so (32) In the absence of the adrenal gland potassium repletion or retention does not result in a rise in blood pressure The administration of cortisone or ACTH will restore the reactivity and tend to raise the pressure (33) Similar effects occur in man (31) For example orthostatic hypotension occurred in a patient who was subject to chronic potassium loss potassium replacement improved the ability to regulate the blood pressure (34)

These hypotensive and asthenic responses are related to the excess renal potassium wastage induced by a high salt intake The sodium conserving function of the kidney is so efficient that this ion tends to be reabsorbed from the glomerular filtrate in the renal tubule however a potassium ion must be excreted by the tubular cells in order to accomplish some of this sodium reabsorption (35 36)

The physiological actions of sodium and potassium balance have long been studied in the isolated heart More recently attention has been called to the ubiquitous redox pump which normally pumps sodium out of the cells while maintaining a high potassium concentration within the protoplasm (37) This action depends on the presence in adequate amounts of potassium in the extracellular fluid For example when the concentration of potassium in fluid surrounding frog skin is diminished the normally high intracellular potassium is diminished while the intracellular sodium which is normally low increases (38) Conway (39) has recently shown that the sodium pump mechanism in yeast cells is more effective when potassium is present in the extra cellular solution DCA appears to weaken the ability of the cell to eliminate sodium from the protoplasm (39)

It is evident that desoxycorticosterone and certain other steroids modify sodium exchange DCA given in large doses to dogs produces hypertension associated with disturbances in salt water balance and this may persist for weeks after cessation of the compound (40) This hypertension is potentiated by a simultaneous administration of sodium salts (41 44) DCA produces an early retention of sodium and water followed by an increased renal loss of these materials Subsequently a sodium appetite and hypertension develop The disturbed sodium balance induced by DCA is evident in tissues other than the kidney since the sweat glands (45) and the terminal ileum (46) also show a reduced sodium excretion Long term DCA administration will ultimately result in a depletion of body potassium with the development of asthenia and a tendency to a fall in blood pressure similar to that produced by excess salt intake The physiological significance of DCA has long been in question However aldosterone has essentially similar physiological effect It is of special interest therefore that arterial hypertension is reported to be associated with a state of mild chronic hyperaldosteronism as indicated by urinary excretion studies (47) Other substances may also produce blood pressure changes Thus Selye has suggested that somatotrophic hormone increases the sensitivity of the rat to salt or to DCA with the induction of hypertension (48) and that other steroids such as methylandrostenediol can raise the blood pressure although this latter hypertension can be prevented by adrenalectomy (49)

When the mechanism of essential hypertension is finally clarified salt and water regulation will probably play a significant role in its pathogenesis The kidney as the ultimate organ involved in electrolyte balance would appear to be a key structure in determining the blood pressure change The adrenal cortical effects on ionic balance and neurohypophysial effects on water exchange probably contribute less directly

SUMMARY

A questionnaire survey of salt intake habit of 126 matched ho pitalized patients revealed that hypertensives were more likely to u e ome or much salt at the table while normotensives generally reported little or none salt usage The hypertensives al o reported they ate regularly (weekly) a larger number of highly alted foods (e g potato chips french fries alt pork ham fish etc) than the number of these foods reported taken by the normo tensives

In experiments on chicks addition of 1 2 percent table salt to the drink ing water or 10 percent salt in the mash resulted in a di tinct ri e in blood pre sure in most of the animals Animals on a high salt limited water intake tended to be stunted in growth and to have a high mortality rate The groups taking the greatest quantity of salt had the highest blood pressures the e animals also showed larger adrenals per unit of body weight

Some mechanisms involved in salt water balance and in blood pressure regulation are discus ed

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DISCUSSION

Dr George A Perera I have everal questions I am troubled about the West Indies becau e on ome of the islands the incidence of glomerulonephritis is high I am troubled that in New York the greater tendency of Negroes to develop hypertensive di ease is limited to malig nant hypertension does an excess of salt affect only one form of hyper tension? When we have corrected for age we have been unable to find any difference in dietary sodium intake or sodium excretion in the urine in hy pertensive versus normoten ive ubjects Dr Podbard did you take age into consideration? I su pect as we get older our dietary habits change

Dr Irvine H Page The a essment of the amount of alt people take is in ome ways ea ier and in ome more difficult than the amount of fat they eat I have tried the interrogation method with many patients and am al together unconvinced that many of their an wers are reliable True there are people who eat extreme amounts or have no taste for it at all and they know it I am concerned with the run of the mine hypertensive patient who has no trong feelings one way or the other

When I was working with Dr Van Slyke at the Rockefeller In titute he in i ted that a daily or tri weekly urinary chloride was the only way to get

an idea of salt intake even when the diet was believed to be rigidly controlled. This I learned to believe after we found a patient getting a large amount of salt from her tooth paste. Thus I hesitate to accept surveys purporting to determine salt intake. Until salt is actually measured I doubt if an epidemiological survey would be meaningful.

As you know, Dr. Corcoran will head an expedition to St. Kitts island to study the incidence of vascular disease and its relation to the diet, especially as it concerns salt intake. We know of the high incidence of strokes in Japanese fishing villages when salt is used as a food preservative in fantastically *large amounts*.

It is too easy to convince yourself of the validity of your own preconceived notions with an epidemiological survey. For instance, a physician in Cleveland is convinced he has shown a direct relationship between hypertension and eating pepper and highly seasoned foods. This summer he published a note showing hypertension could be so produced in rats. Now he is more convinced than ever. You will also recall the supposed relationship to stale coffee. I would therefore plead for much more careful and penetrating epidemiological studies before a stand is taken which then the investigator *feels impelled to defend*.

DR. SIDNEY FRIEDMAN: I too, like Dr. Perera, am puzzled and troubled by a number of things. With Dr. Page I think the association of salt intake with the presence or absence of hypertension is at the moment a matter of association only. We find that if high salt diets are given to rats for sufficient periods of time (three to five months) the hypertension tends to disappear. It is a long jump and a hazardous one from the amount of salt taken in to exactly how the salt is being handled. I think the sodium handling mechanism is of *fundamental* importance and directly determines the state of tonus of the smooth muscle cell. Therefore, salt intake may be essentially determined by the salt output and that saved for the body. It seems rather tricky to try to deduce from measuring one of the parameters exactly what the relationship of the salt intake to the blood pressure level is.

Regarding adrenal size, I have an anatomical bias. I feel it is difficult to decide on the basis of size whether or not an organ is hyperfunctioning. It may be impossible to decide whether a measurement of increase in size should be based on absolute size of that organ related to the animal's age or computed back to the animal's weight. The method chosen may lead to entirely different results, the interpretation of which is determined by personal bias.

DR. GEORGE R. MENEELY: We studied 3,000 human beings in one group and another smaller group. Among the first there was absolutely no correlation between the amount of salt they said they ate and their blood pressures. We did sodium excretion for 24 hour periods on a few of these young draftees and found no correlation with what they said they ate.

The other group came from an industrial plant Industry is becoming highly interested in this question since it is well known that the most valuable employee is the one with years of service and hypertension causes a relatively high loss rate for such employees Some industries which have men working in a hot environment requiring the use of salt tablets are quite concerned about the salt question In this industrial population we did find a correlation between the stated salt intake and the observed blood pressure This group was middle aged similar to that observed by Dahl and all were healthy enough to work Some other groups mentioned here were also selected in that they were patients I believe this selection of special groups is biasing the data on possible relations between human salt intake and blood pressure

DR HENRY A SCHROEDER The question of course is whether you get hypertension by eating salt or you eat more salt because you have hypertension One of the best places to study this matter is where the salt diet is higher than it is here The measured intake of the average Japanese is about ten grams of sodium chloride a day Sodium intake is said to be much higher (up to thirty grams per day) in certain Japanese fishing villages and rural areas At a meeting of the Japanese medical society last Spring I asked about twenty five people if they had measured urinary output of sodium or chloride in hypertensive and normal people to find out how much sodium they did eat and nobody had The Japanese had a habit of feeding soldiers extra salt in Manchuria in cold weather because studies showed that this practice raised the metabolic rate The Japanese have more hypertension in some age groups particularly in women over forty than we do statistically and about as much as we have in other age groups

About two years ago Dr Homer Smith said there was one thing we knew about the hypertensive kidney — and much of this comes from Dr Hoobler s laboratory — that it a salt losing kidney Now if it is a salt losing kidney and if as we believe the sea within us is constant and must remain a constant or we will get sick like Dr Rodbard s dogs with low serum sodium levels then if we lose salt we have to eat more salt This is a question that must be studied more extensively

DR ARTHUR M FISHBERG The percentage of patients with essential hypertension in the hospital in which I work and in my private practice who develop malignant hypertension has decreased steadily over the last twenty years This experience is contrary to that in some municipal hospitals particularly those that care for a large number of Negro patients I now find it difficult to find patients with papilledema in the malignant phase of essential hypertension to demonstrate for didactic purposes The only explanation I can offer is this the private patient and also the type of ward patient we have do not eat much salt Doctors and newspapers have taught them salt is bad for them While not on a low sodium diet certainly not

on any approach to a 200 mg figure they consume far less salt than before The decrease in the proportion of patient with essential hypertension who enter the malignant phase long antedated the widespread use of antihypertensive drugs but has been accelerated since

As regards heredity my experience differs with that of Dr Rodbard perhaps because histories are more easily obtainable In my material the enormous importance of the genetic factor in the causation of essential hypertension is clearly discernible

Dr John H Moyer I would like to refer back to basic mechanism About two years ago we studied the effects of saline infusions over a prolonged period of time in lightly anesthetized dogs Our mortality rate was extremely high climbing to eighty percent after an infusion of twelve hours or more When we used five percent glucose it was probably less than ten percent which raises a question which I pose here In postulating that the effect of salt in hypertension is a direct one on the blood vessels why is the central nervous system always overlooked? Sodium retention may actually increase sympathomimetic activity and hypothalamic imbalance In the experiments I just mentioned I feel these dogs died a central nervous system death We observed some rise in blood pressure followed by vascular collapse not associated with pulmonary edema

Secondly I want to outline a simple experiment for Dr Page if he plans to attend the forthcoming Bahamas medical conference He and his colleagues should have their blood pressures taken every day for two weeks before departure At the conference they should drink tap water and record blood pressures for two weeks while drinking this water which has such a high sodium content When I was there last year I developed moderately severe edema of the ankles Out of interest I recorded the blood pressure I do not believe I have ever had a systolic blood pressure of over 120 before in my life but it was 135 mm Hg and remained so for about ten days after I left Nassau and returned to the States

Dr G M C Masson I would like to expand the remarks concerning the relationship of hypertension and the handling of salt regarding the susceptibility of various animal species to salt hypertension or to desoxycorticosterone hypertension which is a kind of salt hypertension The most susceptible are the chick and rat which respond to salt by a severe and rapidly progressive type of hypertension The dog is relatively refractory to salt hypertension With large doses of desoxycorticosterone or of some of the highly active synthetic steroids the most that can be obtained is a rise of 20 to 50 mm Hg even if the animals have been adrenalectomized They never show malignant hypertension In the rabbit salt and desoxycorticosterone cause hypotension instead of hypertension These examples show that handling of salt is more important than salt intake

DR. SIMON RODBARD Many more problems have been raised than can be answered in the time available Dr Perera mentioned a high incidence of glomerulonephritis in the West Indies I have no personal data on this but Drs Moser Hoobler and associates are investigating this

The validity of questionnaires their value in the study of an epidemiological problem and the association of specific sets of data and a given disease are always subject to careful evaluation Correlations in a given survey may have only an accidental relation with the disease we must face this risk in any research study of any nature The questions we asked were prepared only after extensive consultation with experienced epidemiologists Pairing of patients served to reduce chance associations The correlations proved nothing concerning the relationship between salt intake and the occurrence of hypertension but they do point clearly to the need for more definitive studies on the salt hypertension question

Our data showed no hereditary predisposition to hypertension While the questionnaire has limitations it is more adequate than the drawing of conclusions on the basis of individual cases In any event the relation of heredity and hypertension is far from clear and this includes analysis of clinical data in the literature

Possible errors due to faulty memory of the patient as to what he eats are difficult to evaluate It is hard enough to get valid information when the patient is on the metabolic ward of a research hospital Our data can have meaning even if they represent only an ingestion fantasy or wish or guilt on the part of the patient

It appears that many people living on the smaller islands do take large amounts of salt Dr Schroeder's comments are quite instructive In this regard it is of some value to reconsider our judgments concerning normal blood pressure levels of a given cultural group Perhaps our criteria of normal pressures belong only to our own part of the world

Dr Masson raises the question of species variability which becomes quite evident when we remember that even a low diastolic pressure in the chick is a severe hypertension for most mammals including man Malignant hypertension is quite easy to induce in the dog but we have never seen it in the chick

In answer to Dr Sidney Friedman the weight of the adrenal gland was definitely increased in our salt fed animals especially when compared with body weight This appears to be a more satisfactory basis of comparison than calculating the size of the actual gland against the size of a presumed normal animal Whether the hypertrophy is associated with hyperactivity *is not known*

The remainder of our discussions in this conference will I hope provide definitive answers for some of the questions which have been raised

SODIUM AND WATER RATIOS IN THE PATHOGENESIS OF HYPERTENSION

LEO A SAPIRSTEIN

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THAT there is a disturbance in the metabolism of sodium and water in human and experimental hypertension has been suggested repeatedly Unfortunately the nature of the disturbance is not so clear as one might wish The hypertensive subject is said to show an increased salt appetite (1) but the renal hypertensive rat shows salt aversion (2) (3) Intracellular sodium has been reported increased in hypertensive animals (4) and men (5) other studies indicate it is decreased in experimental hypertension (6) Some work suggests that sodium excretion is depressed in experimental renal hypertension (7) other investigations imply that the hypertensive animal or patient is actually a salt loser (8) (9) (10)

In an attempt to reconcile some of these observations I will show that a preponderance of the evidence indicates that in hypertensive rats there is an imbalance between sodium intake and sodium output which predispose toward sodium retention I will also show that this imbalance cannot be described properly unless the sodium balance is related to the balance of water

Obviously in a chronic condition there cannot be a continuing imbalance between the intake and output of sodium A previous period of imbalance may leave its imprint on the body s sodium content and concentration but this may be concealed in a short term metabolic study

For the most part a history of positive sodium balance cannot be obtained practically Instead we must rely on evidence which suggests that increased sodium intake has exceeded the excretory capacity or that damage to the excretory mechanism has reduced the excretory capacity below normal Only direct determination of body sodium can demonstrate a pre existing positive balance of sodium if indeed such exists

Much data is available indicating that excessive ingestion of sodium presumably above the level which can be effectively excreted induces hypertension

McQuarrie (11) first reported the development of hypertension after giving massive doses of sodium chloride to diabetic children Later Lenel Rodbard and Katz (12) *described the rapid development of hypertension in the* chicken receiving isotonic or hypertonic saline in its drinking water Sapirstein Brandt and Drury (13) made rats hypertensive by substituting hypertonic (2 percent) saline for drinking water These results were confirmed by

Mason and Corcoran (14) and by Mucio *et al* (15). Meneely (16) demonstrated the occurrence of hypertension in the rat exposed to a high salt diet.

The clear relationship demonstrated by Dahl and Love between the subjective evaluation of salt consumption in man and the incidence of hypertension suggests that the adult human subject may be similarly affected by excessive salt intake. The epidemiologic studies of Moser (17) among the natives of the Bahamas, whose well water contains large quantities of sodium chloride and who display an extraordinarily high incidence of hypertensive disease, are also impressive. *However, there is also a very high proportion* of hypertensive disease among the Virgin Islanders (18) who are said to use rain water rather than well water for drinking and cooking.

There is ample evidence to suggest that the sodium content of the body is increased in the animal made hypertensive by renal manipulation or salt loading. This phenomenon was first noted by Eichelberger (19) in the muscles of renal hypertensive dogs. Laramore and Grollman (20) later described an increase in the sodium concentration of most organs in renal hypertensive rats. Similar findings were reported by Greene and Sapirstein in the renal hypertensive rat (4). Mucio *et al* (15) reported very substantial increases in the salt content of the skeletal muscles, heart and liver of rats made hypertensive by salt feeding. Tobian (21) and Tobian and Binion (22) (23) found increased concentrations of sodium in the aortas of hypertensive human subjects and renal hypertensive rats.

When sufficiently large groups of hypertensive animals or patients are studied, a tendency for the plasma sodium concentration to be elevated is almost universally found (Kylin and Elmquist 24, Holley *et al* 25 and Fregly *et al* 26). *Disappointingly the changes are small.* The biological significance of such findings must remain in doubt, particularly when one notes the failure of rats exposed to kidney encapsulation at an older age to show elevation in serum sodium (26).

Are reported increases in organ sodium content of biological significance? Grollman and his associates (27) (28) have shown a clear increase in the mannitol and radiosulfate spaces of hypertensive dogs and men; the same has been noted by Ross (5). Since only slight elevation of extracellular fluid volume is required to increase greatly the sodium content of tissues and organs, the possibility that these increases are due to a minimal edema cannot be ruled out with certainty. It seems improbable that expansion of the extracellular space could have any but a casual relationship to the hypertensive process, particularly when we remember that spontaneous edema and isotonic sodium chloride loading (29) are without important effects on the arterial pressure.

Ross studies (5) suggest that the excess exchangeable sodium of hypertensive men may be intracellular, but the possibility that the excess is all sequestered in bone, though considered, was not ruled out. The work of

Ledingham (6) indicating that intracellular sodium may actually be de pre- ed in the hypertensive heart and keletal mu cle is also di turbing In a small series Moore *et al* (30) failed to demon trate that exchangeable odium of the body was elevated in hypertensives

The chance that the hyperten ive subject may have a decreased ability to excrete odium receives very little experimental support Except for one tudy in renal hypertensive dogs (7) the opposite appears true On the other hand as will be shown below an excretory deficiency toward sodium can be uncovered in the hyperten ive rat or human ubject but only when water reten ion is simultaneou ly considered

Braun Menendez description of the water and chloride excretion of the fa ting hyperten ive rat is especially illuminating (31) Chloride ex cretion of the hypertensive rat did not differ appreciably from that of the normotensive the hyperten ives however howed considerable polyuria In effect though the hyperten ive urine contained about the same *amount* of chloride a the normoten ive it was being excreted at a much lower con *centration*

Some elementary con iderations may be helpful at this point If one con siders that the cells of the body are bathed in an environment of iso o motic alt it is clearly of much less concern to the e cells whether the volume of the environment changes than whether the composition of the environ ment is altered It would appear unlikely *a priori* that iso osmolar volume changes in the extracellular fluid would produce significant physiological effect When changes in o molarity occur however one might reasonably anticipate that the cells would react Thus a lo s of sodium in hyperosmolar solution re ulting in hypo o molar contraction of body fluids might logi cally have the same physiological effect as gain of water without odium re sulting in hypo o molar expansion Similarly odium gains in exce s of water producing hypero molar expan ion of the body fluids might be ex pected to have the ame cellular effects as water lo es in excess of sodium producing hypero molar contraction of body fluid

Although in a qualitative sen e these propo itions are elf evident it is sometimes difficult from a cur ory examination of the sodium and water balances of the organism to determine the tatus of the fluids remaining in the body For example it is not immediately obvious whether an individual losing 100 meq of odium chloride in a liter of urine has uffered a great a di tortion in body fluids as one who has lo t 150 odium meq in two liters of urine

A simple formula fundamentally imilar to that of West & Rapoport (32) *to describe the water economy of the kidney in osmotic loading relates the* behavior of sodium to water in its effect on body fluid The odium aved for the body through renal formation of urine is the product of the urine volume and the difference between the pla ma odium and urinary sodium

concentrations The sodium so described is sodium in excess of water — in effect free sodium The sign of free sodium may be positive signifying that the kidney has conserved sodium in excess of water or negative meaning the body has lost more sodium than water through the kidney

In the example cited above as using a plasma concentration of 150 meq Na per liter the free sodium change represented by the loss of a liter of urine containing 100 meq/l is +50 meq of sodium The individual losing 150 meq Na in two liters of urine has a positive free sodium balance of 150 meq Although sodium losses of the second individual exceed those of the first free sodium saved to the body is much greater in the second In effect he is in negative sodium balance compared to the first on the basis of mass of sodium lost but when the simultaneous water losses are considered he is in a positive sodium balance with respect to water when compared with the first individual

When the studies on urinary excretion of salt and water are analyzed in this light a rather striking consistency emerges For example Green (8) has shown that hypertensive patients are salt losers But the salt losses under basal conditions or loading with isotonic saline are associated with disproportionately large losses of water in the hypertensive group when the free sodium calculation is made the hypertensive group is seen to be in positive free sodium balance though they are at the same time in negative balance of sodium

The data of Weller Cottier and Hoobler (33) are quite similar to those of Green and may be amenable to the same interpretation

TABLE I

WATER AND SODIUM LOSSES BY HYPERTENSIVE AND NORMAL RATS

(12 Hour Metabolic Period)
No Load

10 Hypertensives			10 Normals		
$U_{Na}V$	V	F_{Na}	$U_{Na}V$	V	F_{Na}
meq	ml	meq	meq	ml	meq
2.87	27	1.20	1.72	7	-0.65

Difference HT − N = 1.85 meq F_{Na}

Applying the same principles to chloride the findings of Birchall *et al* (9) reveal an identical pattern Although chloride excretion is three times greater in the hypertensive than in the normotensive subject the free chloride status shows the normals in negative balance for this ion (with respect to water) while the hypertensives are in positive balance

Ledingham (6) indicating that intracellular sodium may actually be depressed in the hypertensive heart and skeletal muscle is also disturbing In a small series Moore *et al* (30) failed to demonstrate that exchangeable sodium of the body was elevated in hypertensives

The chance that the hypertensive subject may have a decreased ability to excrete sodium receives very little experimental support Except for one study in renal hypertensive dogs (7) the opposite appears true On the other hand as will be shown below an excretory deficiency toward sodium can be uncovered in the hypertensive rat or human subject but only when water retention is simultaneously considered

Braun Menendez description of the water and chloride excretion of the fasting hypertensive rat is especially illuminating (31) Chloride excretion of the hypertensive rat did not differ appreciably from that of the normotensive the hypertensives however showed considerable polyuria In effect though the hypertensive urine contained about the same *amount* of chloride as the normotensive it was being excreted at a much lower concentration

Some elementary considerations may be helpful at this point If one considers that the cells of the body are bathed in an environment of iso osmotic salt it is clearly of much less concern to these cells whether the volume of the environment changes than whether the composition of the environment is altered It would appear unlikely *a priori* that iso osmolar volume changes in the extracellular fluid would produce significant physiological effects When changes in osmolarity occur however one might reasonably anticipate that the cells would react Thus a loss of sodium in hyperosmolar solution resulting in hypo osmolar contraction of body fluids might logically have the same physiological effect as gain of water without sodium resulting in hypo osmolar expansion Similarly sodium gains in excess of water producing hyperosmolar expansion of the body fluids might be expected to have the same cellular effects as water losses in excess of sodium producing hyperosmolar contraction of body fluids

Although in a qualitative sense these propositions are self evident it is sometimes difficult from a cursory examination of the sodium and water balances of the organism to determine the status of the fluids remaining in the body For example it is not immediately obvious whether an individual losing 100 meq of sodium chloride in a liter of urine has suffered as great a distortion in body fluids as one who has lost 150 sodium meq in two liters of urine

A simple formula fundamentally similar to that of West & Rapoport (32) to describe the water economy of the kidney in osmotic loading relates the behavior of sodium to water in its effect on body fluids The sodium saved for the body through renal formation of urine is the product of the urine volume and the difference between the plasma sodium and urinary sodium

TABLE IV

WATER AND SODIUM LOSSES BY HYPERTENSIVE AND NORMAL RATS LOADED WITH 1.5% NaCl
(6 hours)

17 Hypertensives			17 Normotensives		
$U_{Na}V$	V	F_{Na}	$U_{Na}V$	V	F_{Na}
meq	*ml*	*meq*	*meq*	*ml*	*meq*
41.4	154	-18.3	57.5	108	-21.2

Difference HT — N = 2.9 meq F_{Na}

plausible picture of the hypertensive disturbance evolves. One may speculate that the basic disorder in hypertension is that the body fluids are always *on the verge of hyperosmolarity. This teetering on the brink may result from* hyperosmolar loading due to an excessive intake or production of osmotically active substances; alternatively, such loading may result during normal intake and production of solutes because of diminished water intake. Even when the water intake and production and ingestion of solutes are normal, the kidney's damaged ability to save water for the body may induce hyperosmolarity of the body fluids.

Ancillary evidence in support of this hypothesis comes from the finding of Ellis and Grollman (35) that hypertensive dogs and men show increased urinary levels of antidiuretic hormone. The lowered water content and elevated cation content of the organs of salt hypertensive rats (15) and the higher cation and nitrogen content of rats with renal hypertension (4) are consistent with this view.

Against this theory is the fact that hypertension can persist in human subjects in the presence of hyponatremia. Peripheral resistance may not be increased in such subjects, however, since the cardiac output is not known. The higher than normal water content of hypertensive organs (20, 23) appears to argue against the hypothesis of hyperosmolarity. But when it is recalled that slight expansion of the extracellular fluid, which has a much higher water concentration than intracellular fluid, will produce such changes without change in osmolar status, it becomes questionable if water content of tissues gives useful information regarding the hydration of cells.

One wonders whether in hypertension treatment should not be directed to the possibility that the presumed defect in the regulation of osmolarity may be remedied by increasing water intake rather than by decreasing the intake of salt, which is after all only one of the osmotic loads placed on the kidney. To this writer's knowledge no studies have been made on this point.

SUMMARY AND CONCLUSIONS

There is much evidence to indicate that hypertension is associated with abnormal accumulations of odium in the body At the same time it appears that both human hypertensives and renal hypertensive animals actually excrete more odium in any given experimental circumstance than normotensives

The apparent paradox can be re olved by relating the sodium economy of the body to its water economy When this is done it is almost consistently een that hypertensives though they lo e odium in excess of normotensives al o lo e water in exce s of normotensives These abnormalities in excretion are uch that relatively more water is lo t than sodium o that the hypertensive subject or animal does tend to accumulate odium at lea t with re pect to water

It is sugge ted that hypertension may follow hyperosmolarity of the body fluids whether this is induced by loading with hypertonic salt re triction of water or a renal inability to con erve water in relation to *o motically active olutes*

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DISCUSSION

DR SIMON RODBARD In the work I described this morning it was shown that chickens feeding on ten percent salt and re tricted as to water intake did not develop as much hypertension as did the control animals on an unlimited water intake I wonder how these observations can be recon ciled with Dr Sapir tein views

DR HENRY A SCHROEDER This all inclusive term hypertension

does not represent a uniform group All kinds of renal disease may be present and of any one kind all stages of degeneration of one or both kidneys The ability of the kidneys to handle electrolytes may therefore differ widely from patient to patient This may account for some of your discrepancies Metabolic balance studies of patients on constant intakes of water and salt do not result in dehydration even when water is relatively restricted for long period The group of hypertensive animals may be more uniform than hyperten ive patients but the kidney s ability to handle water and salt and make ammonia probably varies according to the degree of disease or disorder present Al o there are probably several etiologies of hypertension furthering lack of uniformity This theory is fa cinating in regard to experimental animals but it may not make sense in human beings If the hypertensive is really a relative sodium saver although he is actually a sodium waster he must eat more salt becau e he has to have extra salt even though he is saving it relative to his body fluid concentration

DR SIBLEY HOOBLER In our water and sodium excretion studies in which the same individual has been studied at different blood pressure levels or in which hypertension of various etiology has been examined the blood pressure level has correlated reasonably well with sodium and water ex cretion* Also Dr Dustan s work shows in general that when there is an ob structive renal arterial lesion with unilateral reduction in renal arterial pressure sodium and water output on this side are usually reduced Our own belief is that sodium and water excretion can be correlated with the local pressure within the renal artery We know of no clinical or laboratory investigation that contradicts this generalization originally suggested by Selkurt and Shipley in their work on isolated kidneys and we believe in creased sodium and water excretion in hypertension is a function of pressure within the renal artery rather than ome general metabolic disturbance although what arterial pre sure does to kidney cells it may also do to other cells of the body

Since Dr Mo er is not here and he has been quoted several times I hall try to speak for him What you have heard about drinking rain water in the Virgin I lands does not apply to the Bahaman natives Dr Moser went down there and ob erved that in the inhabitants of the Bahamas urine volume and water and salt intake were very high He also found odium output in the urine very high They were not drinking rain water

DR LEO A SAPIRSTEIN As I recall the group on restricted water weighed less than half as much as the group allowed water ad lib It seems probable to me these animals had so great a reduction in plasma volume and cardiac output that an increased peripheral resi tance may have existed and was

Cott r P T., Weller J M., and Hoobler S W
Effect of an intravenous sodium chloride load on renal hemodynamics and elec trolyte excretion in essential hypertension
Univ Mi higan Conf on Hypertension, Circul tion vol 17 April, 19 8 (In press)

not displayed as hypertension simply because the animals were unable to maintain a normal cardiac output

Dr Schroeder states that hypertensive patients in long term metabolic studies stay in water balance I do not think there is any real doubt that this has to be the case Obviously any patient with a chronic disease must remain in balance for any inorganic substance during the course of his disease But patients can differ with respect to internal level of a substance required to achieve balance I believe in any long term balance study on a hypertensive with respect to water and sodium his internal level of water and sodium is quickly adjusted to the level required to maintain balance subsequently

It is true as Dr Schroeder states that hypertensive patients include a varied group That is precisely why it is so remarkable that water wasting in excess of sodium is so regularly reported in the literature I know of only this one exception which occurs under the unphysiological condition of osmotic loading In such loading the free sodium calculation sometimes shows the hypertensive to be gaining less free sodium than the normal However in terms of water economy which is ordinarily the reverse side of free sodium at least when sodium is the principal osmotic load on the kidney the hypertensive still demonstrates his tendency to lose water in excess of osmotically active solute It is a monotonously regular finding not only in hypertensive animals but also in hypertensive men

Although as Dr Schroeder has reported the changes in the alkali metal in the serum are by no means impressive it is not so clear that osmolarity control is preserved as well as the sodium and potassium levels For this freezing point determinations would have to be made I do not know if anyone has done this

Dr Hoobler notes that water and sodium excretion are increased as a function of the pressure in the renal artery I think the issue here is this Are the two increased in proportion to each other? If water excretion is increased more than sodium excretion one can anticipate secondary changes in the organism which could conceivably result in the perpetuation of the hypertension Thus a kidney in a temporarily hypertensive animal might by excreting water in excess of salt duplicate the conditions in an animal ingesting salt in excess of water (which leads to hypertension) This is a perfect setup for a vicious cycle in which a temporary hypertension is converted into a permanent one

I meant to emphasize that Moser had done his work in the Bahama Curiously in the Virgin Islands where rain water is drunk the incidence of hypertension is also very high In a way the two stories supplement each other In the Bahamas Moser notes the natives drink much salt water and suffer from constant thirst in the Virgin the natives drink a little but of fresh water and are perpetually short of it The common denominator of the two seems to be not excess of salt but shortage of water free of salt

EXPLORATION OF RENAL EXCRETORY MECHANISMS WITH RADIOACTIVE SODIUM AND POTASSIUM

FRANCIS P CHINARD, M D

Departments of Medicine and Physiological Chemistry, The Johns Hopkins School of Medicine and the Medical Division, Baltimore City Hospitals Baltimore Md

During the past twenty years a spate of publications has appeared on renal functions in health in disease and in frequently drastic experimental situations What may be called the grosser aspects are firmly delineated We know what to expect clinically from deficiencies or excesses of certain endocrine products from deficiencies or excesses of various components of the diet from certain types of structural damage and even from changes of posture Changes in the handling of water and of sodium by hypertensive individual and animals are under intensive scrutiny There is for example the recent striking application of experimental studies as a diagnostic tool in determining the management of patients with hypertension and one type of unilateral renal disease (1 2)

In substance there is available a large body of empirical and practical knowledge Interpretations of these data and of studies of species other than man have led to rather definite classical concepts of the complex mechanisms involved in the renal handling of sodium water and other substances As new experimental facts emerge the validity of these concepts is questioned Procrustean techniques may be required if the concepts are not to be modified

What follows is a progress report on continuing experimental studies in dogs of certain features of the renal handling of sodium potassium and certain other substances Because the techniques and procedures used have not received wide application these are described below and some of the results obtained in studies with substances other than sodium and potassium are outlined briefly *

EXPERIMENTAL PROCEDURE

Anesthetized mongrel dogs are used as subjects Infusions are given via catheter in a jugular vein When required a midline abdominal incision i

*These studies have been carried out in collaboration with Dr Theodore Enn[illegible] Dr W Rowland Taylor and Mrs Mary F Nolan and have been generously supported by the Life Insurance Medical Research Fund the Markle Foundation the Veterans Administration the United States Public Health Service the United States Atomic Energy Commission Eli Lilly and Company and Merck Sharp and Dohme The assistance of Miss C L Le[illegible] Mrs B Gre[illegible]n Miss W H[illegible]u Mr A McCoy and Mr J Armant in the course of these studies is gratefully acknowledged For earlier reports and certain procedural detail see references (3) to (8) The results shown in Figures 2 4 a[illegible] 1 8 0 [illegible]e from unpublished stud[illegible]

made and a catheter is inserted into the left renal via the inferior vena cava and tied in place Blood is drawn through the catheter by means of a pump The bladder is exposed opened and a catheter is tied in place in each ureter A left flank incision is made and by retroperitoneal approach the aorta and left renal artery are exposed Injection of test solutions is made through a bent needle in erted into the aorta and turned up into the renal artery

The injection solution contains the blue dye T 1824 which is assumed not to leave the circulation to a significant extent on passage through the kidney a glomerular substance such as inulin or creatinine which is neither ecreted nor reab orbed by the tubules and the appropriate test substances The injection is made in less than two seconds Following the injection some thirty samples of blood are obtained from the renal vein catheter over a period of about one minute Thirty or more samples of urine are obtained from each ureteral catheter separately over a total period of five to twenty minutes

RESULTS

Glomerular substances

Before applying the procedures to other sub tances it was necessary to how that on passage down the tubules diffusion effects were minimal and that little or no separation of glomerular substances occurred Pairs of glomerular substances were tested and results of the type shown in Fig 1a for inulin and creatinine were obtained The ordinates indicate the fractional excretion in each sample of urine for each substance ample number after injection is given along the abscissae The effects of recirculation are evident in that there is significant excretion of inulin and creatinine from the right kidney Accordingly correction for this is made by subtraction of the amounts excreted in each sample by the right kidney from the amounts excreted in corresponding ample by the left kidney The re ultant values are then plotted to give the excretion curves or patterns shown in Fig 1b There is little difference between the two curves similar results were obtained in other experiments (3) There is no evidence of sub tantial separation of the glomerular substances on passage down the tubules

Virtual volumes

It was oon noted that the po itions of these excretion patterns varied with the rate of urine flow More specifically the appearance times the modal (peak) transit times and the mean transit times (9) all were dependent on the rate of urine flow The variation of appearance time with urine flow had already been well documented (10) further our pro cedure was not sufficiently refined (the duration of each urine collection period was too long) to permit obtaining data of the requisite accuracy Accordingly attention was focused on the mean transit times The product of the mean transit time and the urine flow ha the dimensions of a volume The relation hip of these volumes o calculated to the rate of urine flow is

shown in Fig 2 (see (4) for earlier data) The volumes are roughly twice the urine flow

Similar calculations are made in studies of the circulation by the dye dilution method A vascular volume between the point of injection and the point of sampling is calculated from the mean circulation time and the car

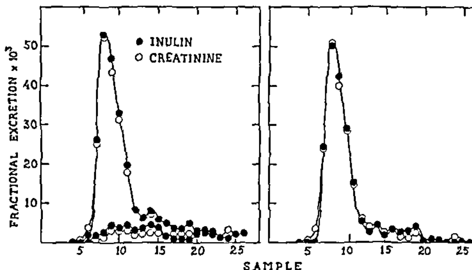


Fig 1a Excretion patterns of creatinine (circles) and of inulin (dots) following injection of a solution containing both substances into the left renal artery The upper curve is for the fractional excretion from the left kidney the lower curves are for the fractional excretions from the right kidney Each sample represents a 12 second collection period

Fig 1b Excretion patterns of creatinine (circles) and of inulin (dots) after correction for recirculation Data from experiment shown in Fig 1a Data from this experiment are from ref (3) and are reproduced by permission of the editors of *The American Journal of Physiology*

diac output or flow These calculated volumes obtained from data with glomerular substances might then be similarly considered to represent the volume of urine between the glomeruli (the transit time from renal artery to the glomeruli is quite small) and the end of the ureters (correction has been made for the catheter volumes) No correction has been attempted for the volumes in the ureters (probably quite small compared to the urine flow because of the rapid peristalsis) and for the volumes in the renal pelves Nonetheless this implied relationship between urine flow and volume of urine in the kidney may have its counterpart in histological observations The columnar epithelium is reportedly flat and the lumen large in tubules from kidneys excreting urine at a high rate of flow the epithelium is raised and the lumen is inconspicuous in tubules from kidneys excreting urine at

a low rate of flow* Possibly the functional variations observed at very high rates of urine flow as in osmotic diuresis may be related to these presumed morphological variations

Apart from these considerations the fact that excretion of the glomerular substances is accomplished not in a very sharp peak but is distributed over

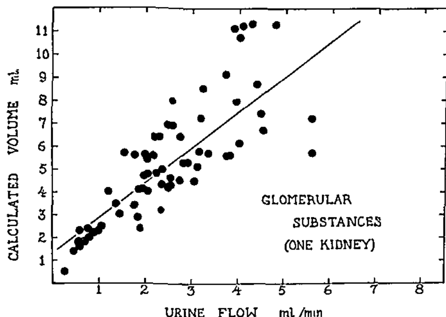


Fig 9 Relationship of calculated volumes for glomerular substances to rate of urine flow *The straight line is regression line V_c on the rate of urine flow* (least squares method) Values given are for one kidney

several minutes and that the injection takes place in less than two seconds points to a dispersion of nephron functions and/or structures As shown later quantitation of this dispersion is possible Also in conventional clearance studies under steady state conditions it might be more appropriate to take as correction for delay time either the modal or the mean transit time rather than the appearance time

Urea

The clearance of urea is substantially lower at all urine flows than the clearance of glomerular substances In the dog and in man there is no evidence pointing to active transport of urea in either direction across the tubule cells That the clearance of urea is lower is apparently the result of simple back diffusion of urea from tubular lumen to peritubular fluid In the type of experiment described above the recovery of urea in the urine should be

*An illustration of these changes is given in "A Textbook of Histology" by A A Maximow and W Bloom 2nd Edition W B Saunders Co Philadelphia 1937 p 47?

le than that of a imultaneou ly injected glomerular sub tance In addi tion there should be some kewing of the urea curve relative to that for a glomerular sub tance some of the urea that had diffu ed from tubular lumen to tubule cell would be expected to diffu e back to the lumen as the front of C 14 labelled urea proceeded di tally down the tubule In Fig 3 are hown the results of an experiment with C 14 labelled urea and creatinine The urea curve is lower than that for creatinine and it is kewed o that the ex cretion of urea is delayed relative to the excretion of creatinine The calcu

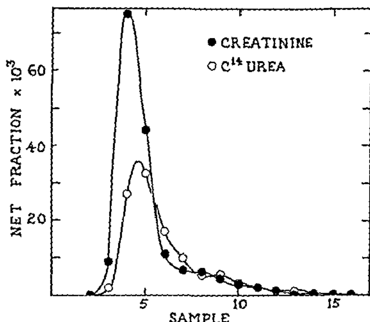


Fig 3 Ex retı n pattern of reatinine (dots) and of C 14 lab lled urea Data f om this experiment are from ref (5) and are reproduced by permiss on of the e l tors of *The Americ n J r rnal of Physiol gy*

lated volume available to urea is greater than the calculated volume available for creatinine In pite of the permeability of cells to urea there is no evidence to permit the uggestion that urea has jumped the gap bet een peritubular fluid and tubular lumen via the back door the excretion of urea is *delayed* relative to the excretion of creatinine Such re ults are compatible with the conventional concept of the renal handling of urea

Reabsorbed substances

Substance which are reab orbed actively by the tubule cells may be con idered to be ecreted from tubular lumen to peritubular fluid — a direction oppo ite to their concentration gradient If reab orption is

complete none of the substance appears in the urine this is what happens with glucose However if an appropriate load of glucose is delivered to the tubules reabsorption is incomplete and glucosuria occurs Under such conditions the excretion curve of C 14 labelled glucose hould be lower than but symmetrical to that of simultaneously injected glomerular sub tance Fig 4 shows the results of an experiment with C 14 labelled glucose and ordinary creatinine under conditions of glucose loading The results are

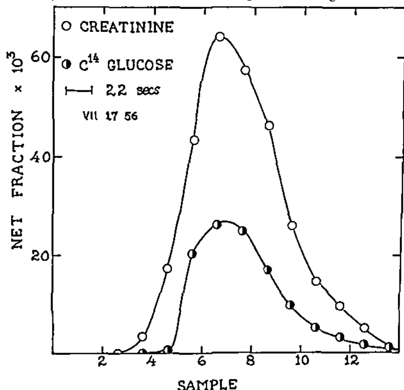


Fig 4 Excretion patterns of creatinine (dots) and of C 14 labelled glucose in presence of glucosuria

e entially as predicted There is however an initial delay in glucose excretion this delay remains to be explained

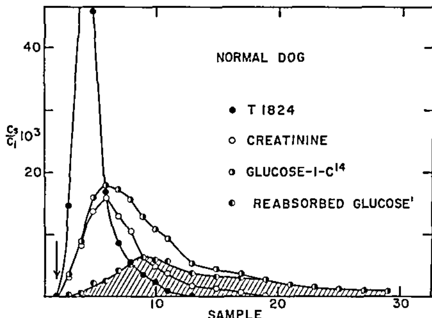
Phlorizin blocks the tubular reabsorption of glucose Following its admini tration the excretion curves of C 14 labelled glucose and of creatinine should be identical The results of such experiments are as predicted though the initial delay in the glucose excretion is again noted

Similar re ults have been obtained with xylo e which is reabsorbed to a much les er extent than glucose

Renal handling of glucose

In conventional clearance studies it has been tacitly assumed that there is relatively little utilization of gluco e by the kidney Various

mechanisms have been propo ed for the tubular reabsorptive proces Breakdown and re ynthe is of the six carbon chain has been uggested In order to te t the several po ibilities a eries of experiments was carried out with glucose the emphasis now being placed on the patterns ob tained in renal venous blood Here the u efulness of T 1824 becomes evi dent Fig 5 hows the results of a typical experiment in which gluco e (label led in the 1 position with C 14) creatinine and T 1824 were injected The ordinates are calculated in the ame manner as in the experiments in which urine was collected The ab cis al cale is different in that the collection of the thirty or more renal venous blood samples is completed in one minute or so in tead of the five to twenty minutes required for the collection of the



F g 5 Renal vein patterns Injection of 1-C 14 glu ose with cre t nine and T 18 4 See text for details. Data are f om ref (7) and are repro luced by permis sion of the editors of *Science*

same number of urine samples The curve for the C 14 labelled glucose i substantially higher than that for creatinine in the later periods That the C 14 activity was associated almo t entirely with gluco e was demonstrated by enzymatic methods and by radioautography That the C 14 activity in all samples had remained in the 1 po ition was demon trated by a combination of *tepwi e chemical and enzymatic degradations of the gluco e* There was no evidence of randomization of the C 14 and hence no evidence of break down and re ynthe is of the 6 carbon chain The recovery of creatinine rela

tive to T 1824 averaged approximately 70 percent while the recovery of glucose averaged approximately 100 percent. It was tempting to suggest that the difference between the glucose and creatinine curves represented glucose transported by the tubules. Evidence substantiating this suggestion was provided by similar experiments carried out after phlorizin had been admin

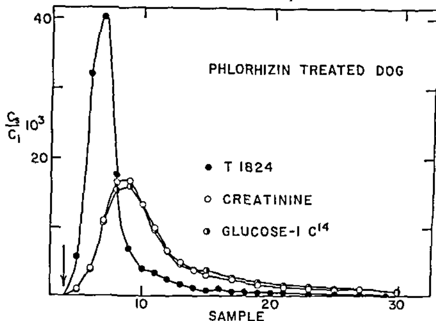


Fig. 6. Renal vein patterns of 1-C14 glucose, creatinine and T 1824 after administration of phlorhizin. Data are from ref. (7) and are reproduced by permission of the editors of *Science*.

istered. Under such conditions the glucose and creatinine curves in renal venous blood should be nearly identical. Fig. 6 shows that this is the case. On the basis of these and similar experiments it was concluded that the glucose was transported with the 6 carbon chain intact and that the differences between the glucose and creatinine curves could be used to construct a recovery curve for the transported glucose. The mean transit time for this moiety of the glucose was about ten seconds greater than the mean transit time for creatinine. The transit time across the tubule cells must then be less than 10 seconds since a few seconds must be required for the glucose in glomerular fluid to travel down to the tubule cells concerned in its reabsorption.

Sources of renal vein carbon dioxide

As indicated, the recoveries of glucose in renal venous blood without prior administration of phlorizin averaged about one hundred percent relative to T 1824. Because of the limitations of the recovery calculation, a more

direct approach was required to determine whether significant degradation of gluco e to carbon dioxide occurred during a ingle circulation through the kidney To this end the renal venous blood amples were collected anaerobically and the carbon dioxide in the e amples was analyzed for radio activity Less than 0 1 percent of the radioactivity injected as C 14 gluco e was recovered as carbon dioxide Gluco e does not contribute significantly to renal vein carbon dioxide under the conditions of the e experiments

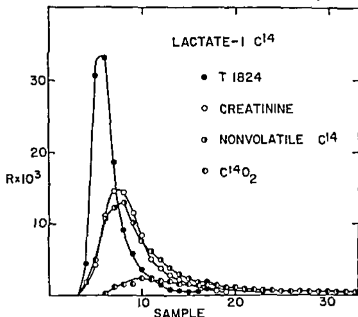


Fig 7 Ren l in p tterns of $C^{14}0$ aft inje tion of l ctate l C 14

The elimination of gluco e as a major direct ource of renal carbon dioxide sugge ted that other potential sources hould be investigated Both lactate and pyruvate have been tried Re ults obtained with C 14 labelled lactate are hown in Fig 7 A ub tantial fraction of the injected radioactivity is recoverable as carbon dioxide The chemical nature of the non volatile C 14 activity has not yet been determined The transit time relation hips permit the calculation of a mean reaction time of about four seconds for the trans formation of lactate to carbon dioxide Similar re ults have been obtained with pyruvate Control experiments involving the injection of labelled bi carbonate into the renal artery have provided omewhat surprising but no unpredictable results there is apparently sub tantial fixation of carbon di oxide by the kidney

These re ults are preliminary However this technique offers the po ibil ity of tudying not only the metabolic activities of organs *in vivo* but al o

tive to T 1824 averaged approximately 70 percent while the recovery of glucose averaged approximately 100 percent It was tempting to sugge t that the difference between the glucose and creatinine curve represented glucose tran ported by the tubules Evidence substantiating this suggestion was pro vided by imilar experiments carried out after phlorizin had been admin

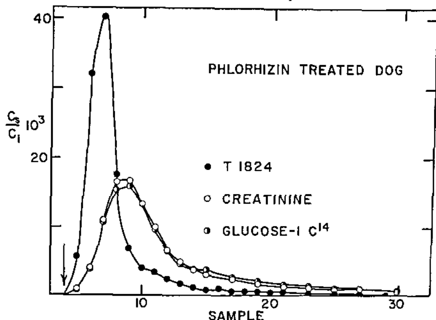


Fig 6 Renal vein patterns of 1 C 14 glucose creatinine and T 18 1 aft r ad mini tration of phlorh in Data are from ref (7) and are reproduced by per mi ion of the editors of *Science*

i tered Under such conditions the glucose and creatinine curves in renal venous blood *hould be nearly identical Fig 6 shows that this is the case* On the basis of these and imilar experiments it was concluded that the glucose was tran ported with the 6 carbon chain intact and that the dif ferences between the glucose and creatinine curves could be used to con truct a recovery curve for the tran ported gluco e The mean transit time for this moiety of the gluco e was about ten econds greater than the mean transit time for creatinine The transit time across the tubule cells must then be less than 10 seconds since a few econds mu t be required for the gluco e in glomerular fluid to travel down to the tubule cell concerned in its re ab orption

Sources of renal vein carbon dioxide

As indicated the recoveries of gluco e in renal venous blood without prior admini tration of phlorizin averaged about one hundred percent relative to T 1824 Because of the limitations of the recovery *calculations a more*

tration the recovery of hippurate in urine is less than that of creatinine possibly because of binding of the hippurate to the plasma proteins The vagaries of the creatinine curve illustrate one of the difficulties encountered with this technique and result from irregular and unequal urine flows from the two kidneys Experiments with PAH and I 131 labelled diodrast have given results which parallel closely those obtained with hippurate

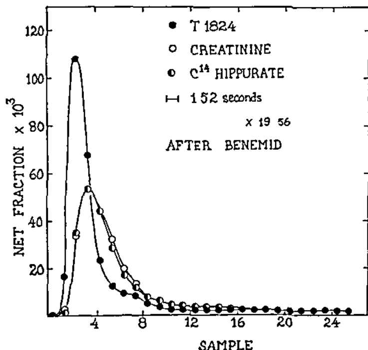


Fig 8b Renal vein patterns of C 14 labelled hippurate creatinine and T-1824 Effects of prior administration of Benemid

Relative to the velocity of urine down the tubules hippurate is brought quite rapidly to the tubule cells by way of the peritubular fluid The delay in excretion of hippurate may therefore be considered in large part a measure of the time required for the secretory process to take place This delay averages about seventy seconds a considerably longer time than is required for the secretion of glucose in the opposite direction It is evidence for the transient storage during the secretory process of hippurate and its congeners in the tubule cells Our results are consistent with those that have led to the development of the I 131 labelled diodrast renal uptake test (11)

The renal handling of potassium

Early ideas about the renal handling of potassium consisted in the simple hypothesis that urinary potassium was filtered potassium that had escaped

tubular reabsorption Occasional clinical reports indicated that the clearance of potassium could be greater than the clearance of inulin or creatinine Because the data were obtained in studies of patients with renal disease the valid

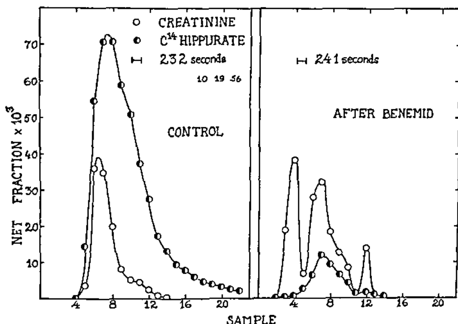


Fig 9 Excretion patterns of creatinine and C 14 labelled hippurate The left panel shows the control experiment The right panel shows the effects of prior administration of Benemid

ity of the inulin clearance as a measure of the glomerular filtration rate was questioned Subsequently Mudge Foulks and Gilman (12) and Berliner and Kennedy (13) demonstrated that under occasionally drastic experimental conditions in dogs the clearance of potassium could be made to exceed substantially the concomitant clearance of creatinine This established that potassium secretion could occur Subsequent work led to the current hypothesis that under ordinary circumstances all the potassium excreted in the urine stems from distal tubular secretion and that all of the potassium crossing the glomerular barrier is reabsorbed by the tubules and returned to peritubular fluid

Further studies particularly those of Black (14) and of Morel (15) showed that there was an extraordinary uptake of radioactive potassium K-42 on a single passage through the kidney and that urinary excretion of this K-42 was related to gradual release from a pool in the kidney rather than to K-42 freshly arriving to the kidney from the renal artery Our own studies confirm these later findings and are consistent with the hypothesis that most of the urinary potassium stems from tubular secretion Figures 10

11 and 13 16 illu trate results of experiments in which both renal venous blood and urine amples were obtained *Fig 10* shows that under the usual conditions of the e experiments there is almost complete uptake of K-42 by the kidney and that there is gradual protracted relea e to renal venous blood

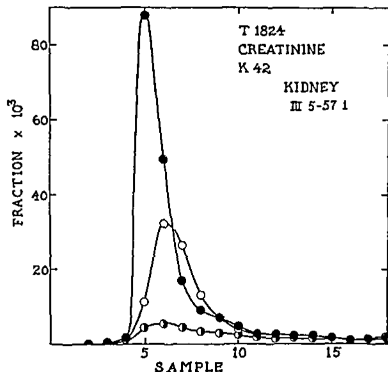


Fig 10 Renal vein patterns of T 18?4 creatinine and K-42 "r" indicates duration of sampling interval

of the K-42 as demon trated by the tailing of the curve Under similar conditions the urine excretion curves how an unusual pattern (Fig 11) There is a peak of K-42 excretion which sub tantially precedes the peak of creatinine excretion Again in the urine there is protracted tailing of the K-42 excretion The pota ium i not all accounted for in the duration of these experiment A large fraction remains in the kidney mainly in the cortex as hown in Fig 12 in which the relative radioactivities of different portions of the kidney are plotted Under conditions of higher potassium clearances the recovery of K-42 in the renal vein is increased (Fig 13) as is the peak of potassium excretion in the urine (Fig 14) Finally under conditions imilar to tho e u ed by Mudge and his collaborators to achieve clearances of

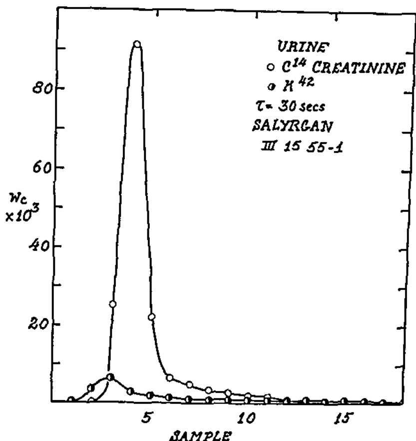


Fig 11 Excretion patterns of creatinine and K-42 after the administration of Salyrgan

ordinary potassium greater than clearances of creatinine (12) the overall uptake by the kidney is further decreased as shown by the greater recovery in renal venous blood (Fig 15) In the urine the K-42 peak is almost as high as the creatinine peak

As indicated these results are consistent with the hypothesis of tubular secretion of potassium The early urine peak may be considered to represent the potassium brought to the distal portions of the nephrons by way of the peritubular fluid thus accounting for the shorter appearance time and modal transit time of potassium relative to the corresponding times for creatinine The secretory process for potassium would then be fast compared to that for PAH and possibly of equal rate to that for glucose The tailing of K 42 in

the renal venous blood and in the urine reflects gradual release from a large potassium pool probably in the more proximal portions of the nephrons* It appears from the rough reciprocal relationship between uptake and excretion of potassium that there may be two distinct potassium pools in the kidney the capacities of which are variable and inversely related Ordinarily the proximal pool has a high capacity and the distal pool a low capacity so that the clearance of potassium is low When the clearance of potassium exceeds the creatinine clearance the capacity of the proximal pool is decreased and that of the distal secretory pool is increased Under the latter conditions the possibility of some contribution to urinary potassium of potassium escaping tubular uptake cannot be excluded by these experiments

The Renal Handling of Sodium

While the results and interpretations just presented may have some novel features by and large they dovetail in satisfactorily with other known facts and concepts about renal functions and metabolism

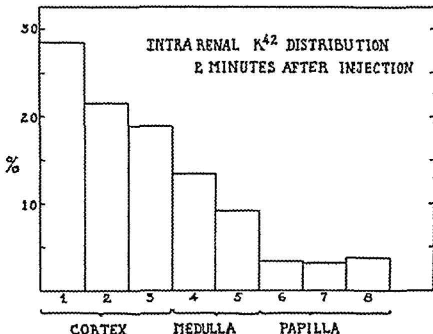


Fig 1 Distribution of K-42 in sections of a kidney removed and frozen in liquid nitrogen two minutes after the injection of K-42 into the renal artery

By a combination of radioautographic and histochemical techniques Eisen and Harris (Nature 180 438 1957) have demonstrated that the retained K-42 two minutes after injection is indeed largely in the proximal tubule cells

Fig. 13 above Renal vein pattern of T 1824 creatinine and K-42 after administration of 3.5% NaCl

Fig. 14 right Excretion patterns of creatinine and K-42 after administration of 3.5% NaCl Data from same experiment as shown in Fig 13

BLOOD
● T-1824
○ C^{14} CREATININE
◐ K^{42}
τ = 1 5 secs
2 % NaCl - 50% UREA
X-9 56

80
60
40
20
$\times 10^3$
5 10 15 20 25 30
SAMPLE

URINE
◐ K^{42}
○ C^{14} CREATININE
F = 7 8 ml / min
τ = 20 secs
2 % NaCl - 50% UREA
X 9 56

16
12
8
4
W_c $\times 10^3$
5 10 15 20 25 30
SAMPLE

Fig 15 left R nal vein patterns of T 18²4 creatinine and K 42 after a lmini tration of ⁷ NaCl and 50 ⁷ urea

Fig 16 above Excretion patterns of creatinine an l K 42 after a lmini tration of ²⁷ NaCl an l 50⁷ urea Data from ame experiment as l own in Fig 15

If urinary sodium is solely sodium that has escaped tubular reabsorption then one would expect to find in the urine a curve for sodium lower than but

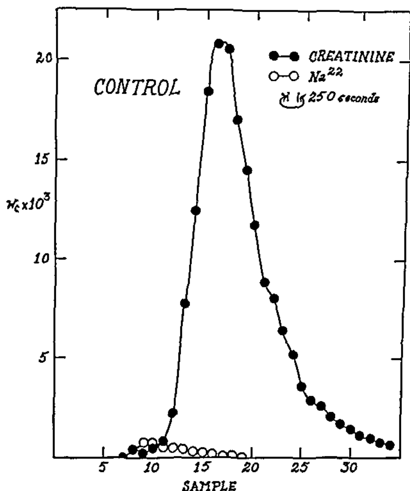


Fig 17 Excretion patterns of radioactive sodium and creatinine Control experiment

symmetrical to that for a simultaneously injected glomerular substance Such a relationship has not been found

Following the simultaneous injection of labelled sodium and of creatinine there is invariably found precession of sodium over creatinine (Fig 17) The appearance time the modal transit time and the mean transit time of sodium are always significantly less than the corresponding times for

glomerular substances When a diuretic such as chlorothiazide (Diuril) was administered following the control experiment just mentioned the peak excretion of sodium was substantially increased and more sodium was ex

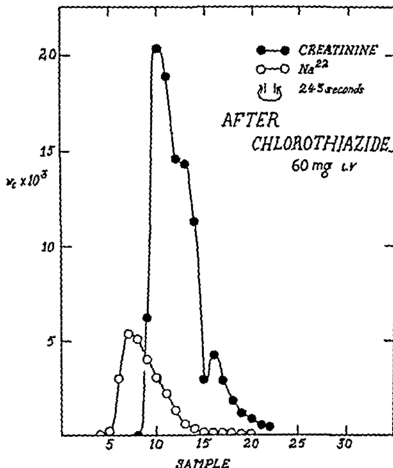


Fig 18 Same after chlorothiazide (Diuril)

creted under the creatinine curve (Fig 18) With mercurial diuretics the peak is increa ed but there is even more excretion under the creatinine curve The sodium curve has however never been found to be higher than the creatinine curve except in the first few samples

Table I summarizes some of the data obtained with radioactive sodium To calculate the values shown in the la t column the total of each ub tance excreted is determined and is a signed the value of 100 The cumulative per

TABLE I

Summary of sodium studies

Type of experiment	Number of experiments	Average percent of injected sodium excreted*	Average percent of creatinine excreted at 50 percent sodium excretion*
Without mercurial diuretic	13	1 6 ± 0 9	8 3 ± 8 3
After mercurial diuretic	8	3 9 ± 2 1	33 1 ± 11 7

*Means and standard deviations

centiles of these totals are then calculated and plotted as ordinates with sample number as abscissal values From the curves connecting the appropriate percentile values the percent of the total eventually excreted creatinine is determined at that time or sample when 50 percent of the total eventually excreted radioactive sodium has been collected in the urine This value permits quantitative assessment of the precession of sodium over creatinine In all experiments this is significant since the mean transit times and the modal transit times for sodium are invariably less than the corresponding transit times for glomerular substances There is scatter However the precession appears to be quantitatively less when a mercurial diuretic is used In paired experiments in which a control run was followed by a run after administration of a mercurial diuretic the precession decreased quantitatively

Figure 19 presents the data from the chlorothiazide experiment in another manner Here the cumulative percentile excretions are plotted as probit units along the ordinates while a logarithmic scale is used for the sample numbers along the abscissae The marked change in urine flow after chlorothiazide was accompanied by a shift of the creatinine curve without a change of slope suggesting that little or no change occurred in the dispersion of this particular nephron function The slope of the sodium curve was changed significantly suggesting that more than one distribution might now be involved in the excretion of the labelled sodium This change of slope is even more marked in experiments in which mercurial diuretics were administered

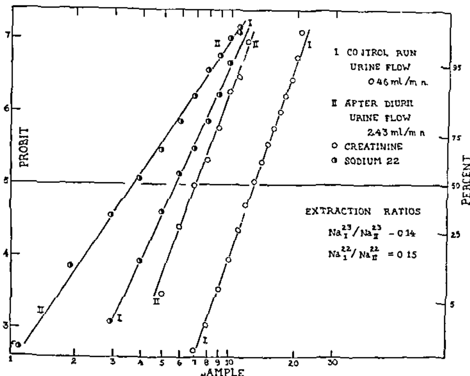


Fig 19 Probit log sample number plot of experiment shown in Figs 1 and 18 See text for details

A matter of some importance is the extraction fraction of ordinary sodium and of labelled odium In this and other similar experiments the extraction fractions have been approximately the same There is no unexpected dilution of the labelled sodium

The data can be summarized in yet another manner by calculation of the virtual volumes for sodium as was done earlier for glomerular substances The values calculated for sodium V_N are smaller than tho e calculated for glomerular ubstances V_G The difference $V_G—V_N$ may repre ent the vol ume of urine in the nephrons between the glomeruli and the ite of delivery of the radioactive sodium into the urine The values found in a eries of experiments are hown in Fig 20 The lowest values for the differences were obtained in experiments in which mercurial diuretics were u ed

Current views on the excretion of sodium can be summarized as follows Analy es of glomerular fluid in amphibia and mammals how that the con centration of odium in this fluid is the ame as that in pla ma within the

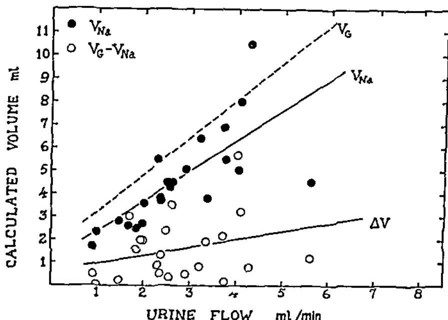


Fig 20 Relationship to urine flow of calculated volumes for sodium (V_{NA}) for creatinine (V_G) and for differences of these values (ΔV) for each experiment The dashed line is the regression line (least squares) of V_G on the urine flow for the experiments shown here and differs slightly from that shown in Fig 3 for these and other experiments The upper line is the regression line of V_{NA} on urine flow the lower line is the regression line of ΔV on urine flow

con traints of the Gibbs Donnan equilibrium Ordinarily the amount of sodium excreted per minute is a small fraction of the amount calculated to cross the glomerular barrier Clearances of sodium greater than concomitant clearances of glomerular substances have not been reported The logical deduction can be made from these facts that excreted sodium is sodium that has escaped tubular reabsorption

The data pre ented above are not compatible with this hypothesis The appearance time the modal transit time and the mean transit time all indi cate that the excreted sodium arrives in the urine in large part via a hort cut or by pass Much of the excreted sodium must cross directly from peri tubular fluid to the tubular lumen It might be suggested that the precession of sodium (which we have also found with radioactive chloride and with or dinary thiocyanate) is simply the result of a diffusion ion-exchange mechan ism and has no bearing on the renal handling of sodium In the case of thio cyanate for example a thiocyanate ion in peritubular fluid would be ex changed for a chloride ion in the tubular lumen thus permitting the thio cyanate ion to e cape into the urine ahead of simultaneously injected creati

nine which must percolate down the tubules With this mechani m it would still be necessary 1) to consider that there was complete reabsorption of thiocyanate crossing with creatinine into glomerular urine and 2) to accept the reality of a short cut or by pass for thiocyanate In addition there is some difficulty in visualizing a simple ion exchange mechanism operating acro s the tructural complexities of the tubule cells Such a mechani m would require permeability of the barrier to sodium chloride and thiocyanate and impermeability to urea urea with a diffusion coefficient nearly as large as the diffusion coefficients of the e ions does not how precession over creatinine *(vide supra)*

In brief we wi h to offer the following as a tentative working hypothesis on the renal handling of sodium Under ordinary conditions of sodium excretion in the dog proximal reabsorption is almost complete the sodium excreted in the urine is added to the tubule urine in the di tal portions of the nephrons by mechanisms quite unknown After administration of a mercurial diuretic there is apparently some escape from reabsorption in the proximal portions of the tubules This hypothesis is strictly applicable only to anesthetized dogs under our experimental conditions We hope to carry out shortly similar but far le s drastic tudies in man

If this hypothesis is correct a revision of the classical views on the renal handling of sodium will be in order and the possibility of tubular ecretion of sodium will have to be considered

SUMMARY

A new technique has been developed for the exploration of various renal functions Injection of test sub tances is made rapidly into a renal artery of anesthetized dogs Some thirty renal venous blood amples are obtained over a period of one minute while a like number of urine samples are obtained from each ureter separately over a period of five to twenty minutes Plots of the fractional recoveries against time after injection provides characteristic recovery or excretion patterns for the individual test ub tances

With pairs of glomerular substances such as inulin and creatinine identical excretion patterns are obtained there is no significant eparation on pa sage down the tubules

The positions of the curves vary with the urine flow From the mean transit times and the urine flows virtual volumes of di tribution between the glomeruli and the end of the ureter are calculated The volumes are approximately twice the urine flows

The excretion curve of urea is delayed with respect to that for creatinine and the recovery of urea is less as expected from the hypothesis of back diffusion of urea

The renal handling of gluco e is examined in ome detail Gluco e is transported across the renal tubule cells with the 6 carbon chain intact It does not contribute significantly directly to renal vein carbon dioxide while

lactate and pyruvate do. In the presence of glucosuria the excretion pattern of C 14 labelled glucose is roughly symmetrical to that for glomerular substances.

The excretion patterns of PAH, hippurate and diodrast are delayed relative to the patterns of glomerular substances. Approximately seventy seconds are required for the movement of these substances across the tubule cells.

Excretion patterns of K-42 reveal that the peak excretion of K-42 precedes the peak excretion of simultaneously injected glomerular substances. There is in addition protracted excretion of the K-42 at a low rate. The recoveries of K 42 in renal venous blood are small, indicating substantial uptake by the kidney tissue. With potassium clearances equal to or exceeding clearances of creatinine renal uptake is decreased but the peak excretion of K 42 is markedly increased. It is suggested that there are two distinct pools for potassium in the kidney of variable and roughly reciprocal capacities. A proximal pool is involved in the uptake while a distal pool is involved in the excretion of potassium.

Excretion patterns of radioactive sodium show a similar precession over *simultaneously injected glomerular substances. Ordinarily the precession* is such that about eight percent of the eventually excreted creatinine is in the urine when fifty percent of the eventually excreted sodium has been collected. The precession of sodium is decreased after mercurial diuretics.

It is suggested that ordinarily most if not all the filtered sodium is reabsorbed and that excreted sodium has been added directly to distal urine from peritubular fluid. After mercurial diuretic some of the excreted sodium may be derived from glomerular fluid by escape from tubular reabsorption.

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DISCUSSION

DR HENRY A SCHROEDER What happened to pota sium after a mercurial diuretic?

DR FRANCIS P CHINARD Diamox alone produces an increa e in the peak pota sium excretion If this is followed by a mercurial uch as Salyrgan the potassium peak becomes decreased as does the fractional excretion of potassium ju t as the clearance of potas ium increased by Diamox is de creased by ub equent administration of a mercurial diuretic

DR LEO A SAPIRSTEIN Do you have evidence of a decrea e in proximal tubular reab orption of odium during o motic loading?

DR FRANCIS P CHINARD After an o motic load there appears to be an increase in the early part of the odium excretion ALo there is evidence that more comes down from the glomeruli no matter what o motic load is used Mannitol for example cau es an increase in both the peak and the later position With sodium sulphate loading the peak is again elevated but

there is still more excretion under the creatinine curve presumably because of the presence of obligatorily excreted anions

DR THOMAS FINDLEY May I ask if you think water could be secreted also?

DR FRANCIS P CHINARD We have done a number of experiments with labeled water but the curves themselves are not very informative because of their spread The appearance time for water is smaller than that for creatinine and about the same as that for sodium and potassium The peak of the water curve is delayed with respect to that of creatinine Presumably some of the water may behave as does urea entering tubule cells from the lumen and returning eventually to the lumen For the water the curve could be broken down into three or more constituent curves Our data do not permit any conclusion as to the possibility of water secretion

DR MEYER FRIEDMAN Any other questions? If not I presume this is the ea within us One undoubtedly could use the inulin clearance just as easily as the creatinine?

DR FRANCIS P CHINARD A series of experiments was carried out in which pairs of glomerular substances were tested The pairs were creatinine and inulin inulin and ferrocyanide and ferrocyanide and creatinine No significant differences were detected in the curves fractional excretions or time parameters of the paired substances

CHRONIC SODIUM CHLORIDE TOXICITY AND THE PROTECTIVE EFFECT OF POTASSIUM CHLORIDE *

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A LEGACY from evolution is an exceptionally good mechanism for water and salt retention and for excess potassium excretion (1) From prerecorded history the need for salt is indicated in the herbivores great treks to salt licks and the carnivores filling their needs from their natural diet of the flesh of other animals (2) Legacies of history are the saline wars slavery decapitation and other strong measures (3 6) Legacies of the 19th century are rich and varied (7) In 1807 Davy isolated potassium and later that same year he isolated sodium also by electrolysis By 1850 Carl Schmidt (8) was reporting determinations of sodium and potassium in the blood in his essay on cholera He and Redtenbacher (7) are commonly credited as the first who paid scientific attention to salt in disease states but as Gamble (9) has pointed out the honor really lies with the London physician O Shaughnessy twenty years earlier In the ensuing hundred years the merit of salt withdrawal in edema heart failure and hypertension has been discovered and rediscovered (10 11) Observations and experiments in the 20th century are more familiar to all of us (12 19) Allen (20) in 1922 considered low sodium diets important in hypertension and the rice diet of Kempner (21) some thirty years later is an example of the widespread application of such theories Selye (22 23) produced nephrosclerosis like lesions in chicks fed large amounts of salt Sapirstein (24) produced renal lesions and hypertension in rats by providing only salted drinking water The minimal sodium requirements for many laboratory animals have been determined and the need for salt for the growth of farm animals is well proven However despite this knowledge little is known of the actual requirements for mammalia and what if any constitutes a toxic level particularly on the basis of long continued intake Our investigations of the possible toxic effects of chronic dietary sodium chloride initially centered on the hypothesis of threshold and the hypothesis of lag Findings early in 1953 focused our attention on the possible relation to potassium intake accordingly life span experiments were started in which the potassium to sodium ratio in the diet was brought toward one

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Early Findings

In the initial experiment started in 1951 six groups of thirty five week old male Sprague Dawley rats housed in constant temperature humidity con trolled quarters were placed on complete purified diets identical except for sodium chloride (25)

A basic ration of 25 1 percent purified Ca ein 51 8 percent sucrose 20 0 percent hydrogenated vegetable oil a complete vitamin mixture and 2 9 percent mineral mixture (26) without added sodium chloride was prepared

SODIUM SPACE

mple	% NaCl	N	$\bar{x}$ Na Space ± S E
2 - 4 months			
ntrol	0 15	7	23 8 ± 0 75
gh salt $\bar{s}$ edema	7 0 8 4 & 9 8	11	26 1 ± 0 61
gh salt $\bar{c}$ edema	7 0 & 9 8	2	57 7
8 10 months			
ntrol	0 15 0 2 & 1 1	28	23 1 ± 0 28
lded salt	5 6	10	24 7 ± 0 65
gh salt	7 0 8 4 & 9 8	40	27 2 ± 0 67

Fig 1 Sodium space measured with Na^{24}

and found to contain 0 01 percent NaCl Diets were derived by the addition of powdered sodium chloride intimately mixed The control diet contained 0 15 percent NaCl The other five groups received progressively higher pro portions of odium chloride 2 8 5 6 7 0 8 4 and 9 8 percent

It is worth noting that the salt content of the 2 8 percent NaCl ration com pares roughly on a weight for nutrient basis with the human intake of about 12 15 grams a day a common e timate of the salt in the diet in this country (27)

The rats had free acce s to tho e diets and in later experiments 1 1 2 0 14 0 and 21 0 percent NaCl as well as demineralized water

When first placed on high odium chloride marked polydipsia and polyuria but only mild anorexia occurred After three days the e rats appeared to be everely dehydrated Two weeks later the rats all looked healthy and were gaining weight regularly

In the initial experiment average weight gains for the first twenty weeks were 353 grams control ration 331 grams 2 8 percent NaCl 315 grams 5 6 percent NaCl 310 grams 7 0 percent NaCl 295 grams 8 4 percent NaCl and 274 grams 9 8 percent NaCl (28) The earliest untoward finding (29) was during the third and fourth months when edema developed in 18 percent

of the rats eating the three highest levels of odium chloride Sudden weight gains of 40 to 160 grams occurred Extracellular water measured with radio active sodium (30) rose from the control level of 24 percent to 58 percent of body weight

The e edematous animals were everely anemic and showed lipemia and hy poproteinemia At autopsy there were obvious edema and anemia Other wi e microscopically all the ti sues except the kidneys appeared normal In relatively bloodless glomerular tufts there were foam cells containing large



Fig 9 Early glomerular lesion (H & E) Reproduced with the permiss on of the Editors of the Journal of Exper mental Medic ne

amounts of fats taining material The tubules exhibited a nephrotic degen eration and contained al o much fat staining material There were les er deposits of lipoid in ome of the arterioles

Three edematous animals urvived this pha e rapidly lo t their extra fluid and became extremely emaciated and cachectic Again all tissues seemed es sentially normal in the gross except the kidney A renal lesion similar to that de cribed above but more extensive was ob erved Many glomerular tufts were obliterated Tubular degeneration was extreme No evidence of adrenal failure was found There was wide spread arteriolar disea e of all the parenchymatous organs (31)

During an eight month period about fifteen percent of the test animals on high alt rations in the fir t and in the six ucceeding experiments de

veloped renal failure Among those which did not there was a high incidence of elevated blood pressure In the animals which developed renal failure massive edema occurred abruptly and sometimes was o extreme that the extracellular fluid (measured with radioactive sodium) accounted for more than one half of the total body weight At this phase the rats were severely anemic hypoproteinemic azotemic lipemic and had elevated blood pressure As I have said three rats in the first experiment lost their extra fluid and entered a state of cachexia Two rats entered this terminal state without developing edema The hearts livers kidneys and adrenal glands usually were hypertrophied The kidneys showed a diffuse degenerative disease in volving all parenchymal elements The glomeruli were fused and almost blood less due to the accumulation of sudanophilic lipid and the degeneration of basement membranes There was evere lipid degeneration of the tubular epithelium The arterioles underwent fatty degeneration and sclerosis (32)

Blood Pressure

Systolic blood pressure measurements were made by the cuff method of Kerston *et al* (33) At the end of the ninth month in the first experiment and as early as the second in later experiments reliable reproducible observations were obtained At the ninth month of Experiment 1 to our immense astonish ment we found an almost perfectly linear relationship between the average blood pressure (the mean for the group) and the amount of salt in the diet (34) There is quite a bit of scattering The highest group those eating nearly ten percent of salt had a mean systolic blood pressure of about 155 but the levels ranged from about 210 down to something under 130 Three months later scattering is less and the mean blood pressure has gone up considerably in all groups

In later experiments (35 38) the association of hypertension and high dietary sodium chloride was evident from the fourth month A total of 622 male and 21 female rats have been subjected to the experimental regimen with increments of NaCl as the sole variable in the purified diet The mean elevations of blood pressure were somewhat less in the female Comparable hypertension was produced in seven females by feeding commercial chow with added NaCl Females eating 5 6 and 9 8 percent sodium chloride mated with normal males and delivered apparently normal young without developing symptoms of eclampsia although the number of pregnancies the sizes of litters and the survival of the young were unfavorably influenced

In addition to the early nephrotic syndrome increa ed sodium space and elevations in systolic blood pressure (30-41) there was evidence of shortened life pan (42) proportional to the levels of NaCl added to the purified diets Other unfavorable physiologic and nutritional threshold and lag effects were noticed (43) Serum cholesterol as measured by the method of Pearson *et al* (44)

r + 54 ± 12

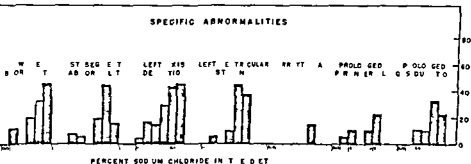
SYSTOLIC BLOOD PRESSURE (MM HG)

240 220 200 180 160 140 120 100

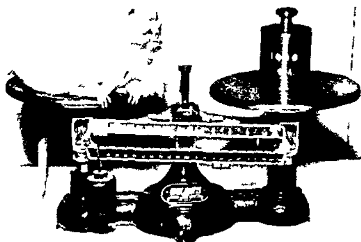
50 100 150 200 250 300 350

SERUM CHOLESTEROL (MG %)

Fig 3 Elevated serum cholesterol not exhibited by normoten ive rats



F g 4 D trib tion of l etroc rdiographic abnorm lities at 19 month



DODSWORTH

0 15% NaCl - AT 20 MONTHS

BLOOD PRESSURE 122 - SERUM CHOLESTEROL 178

Fig 5 Obese rat on control ration normal electrocardiogram

was elevated in young as well as in middle and older aged rats In a blind analysis of 90 electrocardiograms* after nineteen months (corresponding to late middle age) on the experimental regimen the incidence of electrocardio graphic abnormalities paralleled the degree of hypertension and the concentra tion of NaCl intake Rats eating 14 0 percent NaCl were dead at fifteen months those on 21 0 percent at nine months Some eightly percent of the group eating 9 8 percent NaCl (the highest dietary level in this analysis) exhibited abnor malities The electrocardiographic abnormalities in these elderly rats cor related well with hypertension and cardiac hypertrophy at autopsy

Maturity Characteristics (15)

In the nutritional effects as in the physiologic we have consideration of threshold and of lag Early growth and development were adversely affected by the increment of NaCl The highest salt diets 14 0 and 21 0 per

cent resulted in a high mortality threshold early in the course of the experiment. The maximum body weight attained was related to the amount of salt in the diet (46). The mean body weight of the control group was significantly higher than the other groups ($P<0.01$). Obesity most pronounced in the control group was observed in animals at all levels up to and including 5.6 percent NaCl. It was not seen among rats eating 7.0 percent or more of NaCl in the diet. One grossly obese control rat weighed over 1,000 grams at twenty months. His electrocardiogram was within normal limits and his systolic blood pressure 122 mm Hg and total serum cholesterol 178 were very near the mean values of the control group. The control rats continued to gain weight for seventeen months longer though not significantly than the 2.8 percent (fifteen months) and 5.6 percent (sixteen months). In the groups consuming 7.0 percent or more NaCl the average weight gaining period was significantly shorter. The mean systolic blood pressure measured during the month in which the maximum weight was attained was significantly

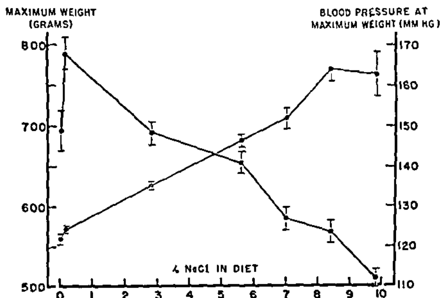


Fig. 6. Blood pressure at maximum weight.

higher ($P<0.01$) in all groups eating added salt. The blood pressure at maximum body weight is not synonymous with the maximum blood pressure exhibited during the life span. This distinction is important in appraising the highest levels of salt feeding as the mean maximum blood pressures attained by these groups were well above the levels exhibited at maximum

MEAN AND STANDARD ERROR OF THE MEAN

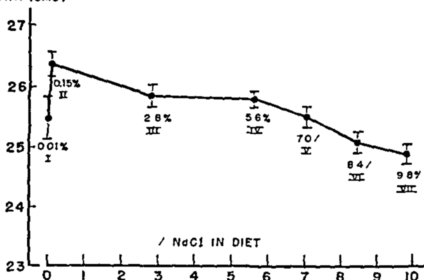


Fig 7 Average length at death — Experiment 1

MONTHS ON DIET

PER CENT SURVIVAL

21% NaCl

14% N Cl

7 0 8 4 +9 8% NaCl

2 8+5 6% NaCl

0 15% N Cl (CONTROL)

Fig 8 Survival curve

weight The average body length at death mea ured from the tip of the n ͵ e to the tail ba e at autopsy followed the maximum weight attained pattern ı e the controls were ıgnificantly larger than groups eating 7 0 percent or more of NaCl

Longevity (42 43, 45, 46)

Twenty one and 14 0 percent NaCl resulted in high mortality early in the cour e of the experiment Decrea ed urvival in the group eating 7 0 9 8 percent NaCl was detectable from the fifth month The other level controls 2 8 and 5 6 percent present the e pecially triking feature of identical survival until the fifteenth or ıxteenth month of expo ure to the diet approximating late maturity or early ene cence It is noteworthy that tho e rats eating 2 8 and 5 6 percent NaCl the levels most rea onably related to human consumption did not die at an exce sive rate until after the seventeenth month. They had been mildly to moderately hypertensive from the ninth month but only this late in life does the lag effect of increa ed dietary salt exact its penalty Considering these experiments on a time schedule adjusted to the human life pan (ten days for rat equal one year for man) benign essential hypertension appears in the third or fourth decade but only in the early fifties is the sur

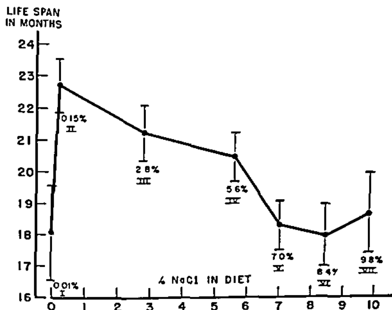


Fig 9 Averag adrenal weight — Experiment I

vival rate noticeably different This is remarkably similar to the pattern the naturally occurring disease follows in the human being

Analysis of data on wet organ weights at death must take into account the variations in body weight and the variations in age of the rats at death Animals less than twelve months old at death were considered as young

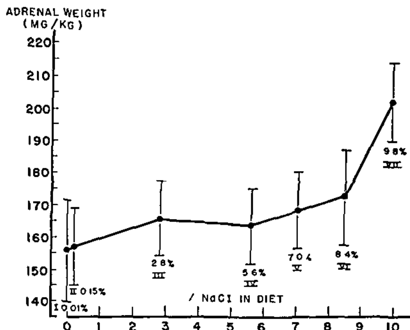


Fig 10 Average life span — Experiment 1

thirteen to nineteen months as middle aged and twenty or more months as old Organ weights were expressed as weight of the organs in grams per kilogram of body weight Mean heart weight increased as the dietary salt intake increased the greate t cardiac hypertrophy being evident at the 9 8 14 0 and 21 0 percent NaCl levels These increments were consistent with the increa es in blood pres ure Relative heart weights in rats dying or sacrificed in youth were similar until the NaCl intake was at the 7 0 percent level After twenty months on the experimental regimen the increased relative cardiac weight is apparent at the 2 8 percent level Renal hypertrophy fol lowed a similar pattern The relative adrenal weight changes were less consi tent The smallest relative adrenal weights were found among the 0 15 percent NaCl control animals and the 2 8 percent NaCl the greatest at intakes of 7 0 21 0 percent NaCl In rats dying during the fir t year increa ed

adrenal size was related to amount of dietary salt A conver e relationship was evidenced in tho e dying after twenty month

The arteriolosclerotic lesions in the fifteen percent of the rats eating high levels of salt which developed the early nephrotic syndrome have been dis cus ed Among the remainder life pan was hortened hypertension developed there was a disturbance of lipid metabolism renal and heart failure occurred all in proportion to the amount of NaCl in the diet The pertrum of hyper tensive cardiova cular renal di ease seen in the human was reproduced rang ing from a clinical course resembling that of mild benign essential hyper tension with minimal shortening of life pan to rapidly progres ive and lethal malignant hypertension

Arteriolar lesions (29 31 32 39 40 41) occurred in incidence extent and degree proportional to the increase in dietary sodium chloride and to the everity of the clinical course In the more advanced disease the renal arterioles were uniformly involved Stainable lipid formed vacuoles in smooth



Fig 11 Glom rular lesion tubular l s on an l arteriolar necros s Reproduced with pe mi s on of the Ed tors of the Journal of E perim nt l Medicine

mu cle cells some of which were necrotic In many arterioles the ela tic lamina was greatly swollen frayed and inten ely eosinophilic The lumina were narrowed or even occluded Visceral arteriolar lesions were fairly con tant among the e animals and were almo t invariably present in the heart pancreas testis and gastrointestinal tract In the less severe forms of the



Fig 12 Arteriolar lesion in testes

disease the vascular le ion both renal and general visceral was less im pressive and less constant usually consisting of medial hypertrophy

Potassium Chloride (47 51)

The highly reproducible significant correlations of dietary alt with systolic blood pressure elevations and hortened life span in the rat offered a sensitive measure of pota sium as an antagoni t and po sible interrelations of dietary sodium and potassium (35)

As you recall in 1843 it was postulated that the herbivores' treks to salt licks were motivated not by the lack of odium in the diet but to the wealth of potassium (52) The fine report of Thompson and McQuarrie (53) in the early 1930 s illustrates the hypertension governing effects of potas ium chloride added to high sodium chloride diets in salt eating children (one as much as sixty four grams daily) They tated *In the ca e of one normal control subject* the inge tion of fifteen grams of odium chloride every six hours cau ed an increa e in blood pressure from 115/80 to 118/100 mm Hg when the subject was on the simple relatively low potassium diet given to *the three diabetic children* but *little or no change* when he was taking an ordinary mixed diet containing liberal amounts of vegetables and meats Priddle (54) in 1943 advocated pota ium as a po sible therapeutic agent in hypertension

Experiments bringing the dietary K Na ratio toward one were initiated in 1953 Concurrent control group and added NaCl groups comprised the

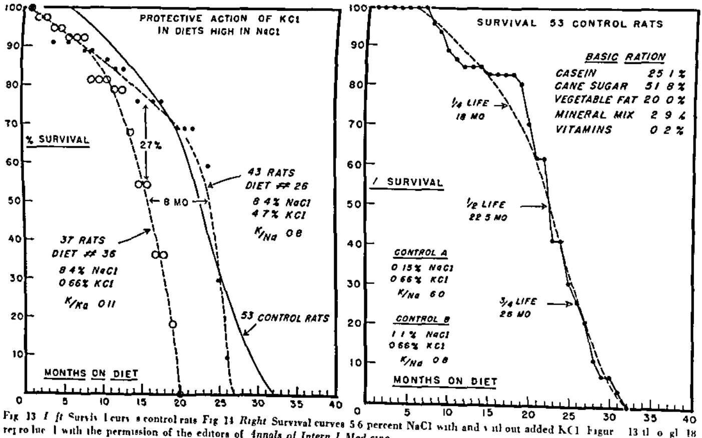


Fig 13 *I ft* Survi l curv s control rats Fig 14 *Right* Survival curves 5 6 percent NaCl with and v it out added KCl Figur 13 tl o gl 18 rej ro luc l with the permission of the editors of *Annals of Intern l Med cine*

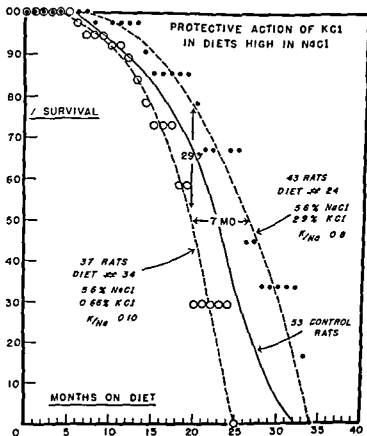


Fig 15 Survival curves 8 4 percent NaCl with and without added KCl

pilot experiment 5 6 percent NaCl + 2 9 percent KCl and 8 4 percent NaCl + 4 7 percent KCl were fed to the rat The la t experiment included rations containing 9 8 percent NaCl and 9 8 percent NaCl + 5 6 percent KCl Let us look fir t at the protection afforded survival At the 5 6 percent level of added salt bringing the K Na ratio toward one enabled the con sumers to outlive not only their counterparts but the concurrent control Less dramatic but still significant was the difference at the 8 4 percent level At 9 8 percent after early decimation by the nephrosis syndrome (the e animals were probably approaching the total electrolyte limit) the potassium protected rats outlived their counterpart After eight to ten months on the

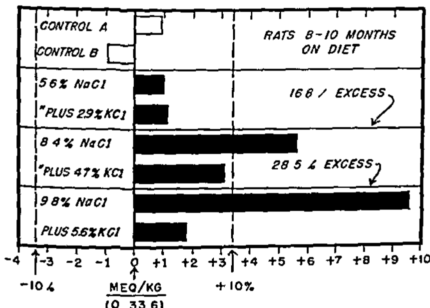


Fig 16 Total exchangeable sod um

regimen measurements of total body odium by i otope dilution in elected rats howed some KCl protection at the 8 4 percent and definite KCl pro tection at the 9 8 percent level of odium chloride

Added potassium chloride had no apparent effect on the modest hyper tension of rats fed at the 5 6 percent NaCl level Blood pres ure elevations were al o present in the groups receiving 8 4 and 9 8 percent odium chloride to which pota ium was added but these did not approach either their

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DISCUSSION

DR HENRY A SCHROEDER I would like to bring out everal important points First Dr Merrill would like to know the level of sodium and pota sium in the plasma on the e high alt diets Your control chole terol values 130 140 are quite high for the rat in our experience and I wonder what method you used We find them u ually around 100 or less

Secondly are not the e lesions merely the nonspecific hypertensive vascular le ions you ee in any form of hypertension?

The third point is that I think it hazardou to imply in any way a relation hip between these mo t unphy iological experiments and the situation in man Many mea urements have been made on normal diet and urine and we believe five to eight grams per day is a normal intake of odium chloride The measured intake in Japanese is ten grams which is less than the equiva lent of the 2 8 percent level in your rat experiments and only a little more than in the American diet There i no evidence measurement wi e that Japane e take larger amounts According to ome old experiment eighteen grams per liter is the mo t a young adult apparently can concentrate in terms of odium chloride Perhaps children can concentrate higher amounts older people concentrate less In Michigan ome years ago Dr Richard Lyons

used thirty grams in young adults and got edema high venous pressure dyspnea and in some signs of cardiomegaly and pulmonary congestion whereas dogs can concentrate to levels many times higher So I think we do not eat as much salt as is thought by Dr Meneely, probably only four five or six grams If you pour salt from a shaker into a spoon instead of on food you realize a gram goes a long way in seasoning food

DR E D FREIS Some arterioles in the histological sections look like hypertensive changes and some like periarteritis nodosa Selye produced periarteritis nodosa in rats Did you see such lesions? Did you measure plasma volume or blood volume in any of these rats on high sodium diets?

DR SIMON RODBARD In the experimental series that we reported yesterday we also fed cholesterol to some of the animals on a high salt diet Our results show the addition of salt alone to animals on a normal mash diet changes neither the plasma cholesterol nor the tendency to atherosclerosis in the aorta or in the coronary vessels However addition of salt to the diet of animals receiving cholesterol definitely intensifies the lesions in these vessels even though the plasma cholesterol level is unaffected I might also add that we saw no changes in the kidney comparable to those reported by Dr Meneely Perhaps this is due to species difference

DR SIDNEY FRIEDMAN We find that if sodium is added to the diet in the absence of potassium the animal becomes severely hypotensive In other words sodium becomes a hypotensive agent in the complete absence of potassium in the diet As Dr Perera suggested rigid restriction of potassium in the diet of essential hypertensive patients produces a moderate reduction in their blood pressure

DR GEORGE A PERERA About one quarter of that in the normal diet

DR ARTHUR M FISHBERG I would like to ask Dr Meneely if the hypercholesterolemia in his experiments always accompanied hypoalbuminemia A great deal of evidence has been brought out here about the role of increased sodium intake in the production of high blood pressure But in treating human hypertensive patients on the ward one often observes that during heart failure they develop hyponatremia and nevertheless the hypertension persists at maximum levels A patient may have a serum sodium of 110 115 milliequivalents for weeks with the blood pressure still at 200/120 This requires reconciliation with the conception of the relation of sodium retention to hypertension

DR GEORGE R MENEELY I feel like one of the scholastics of the Middle Ages I think we have raised more ghosts than we have laid I do not understand many of our findings Our rats were given certain levels of sodium chloride they chose to take certain amounts *of fluid and then certain things* happened The experiment is obviously too vast ever to complete the analysis Therefore we can only regard it as a report of what happens in rats given this particular diet

Obviously our animals were whole animals — they had all their parts The classic example of the extirpation type of experiment concerns the man who said to a flea Jump flea jump The flea jumped and he noted down that the flea can hear commands After pulling the flea s legs off he yelled Jump and the flea did not jump He then put down Removal of legs from fleas makes them deaf

Dr Friedman we have never seen the blood pres ure drift down in high salt eating animals — it always drifts up That the e rats wait eventeen months to manifest their difference from the controls suggests that whatever is going on is a slow process

Dr Schroeder the blood levels of odium and potassium are essentially normal We do have some rather detailed analy es of organ sodium and potassium The method of cholesterol level determination is that of Pearson and associates*

This tandard rat diet is high in fat and our rats get more calories from fat than we wish I am sure the vascular le ions are nonspecific I do not think there is periarteritis We have not seen cellular infiltrate around the small arteries These experiments may be unphysiological They are of course on rats I know nothing about man Adequate figures for human *intake of salt are some of the most needed and least known* My Japane e figure up to thirty grams of salt was pure hearsay It is e sential to find out how much salt people are eating

Our odium space findings are complicated In waterlogged nephrotic rats odium spaces ranged up to fifty or ixty percent of body weight with non edematous high salt rats having larger sodium spaces than controls As life goes on the control sodium paces go down somewhat while the others stay about the same Meanwhile the non salt eating rats become obese This may account for the differences Venous pres ure goes up in rats that develop heart failure

Dr Rodbard I am very interested to hear about the salt and cholesterol effects Our dogs are not becoming hypertensive but they are showing changes in cholesterol With regard to the coincidence of hypoalbuminemia and hyper cholesterolemia that is seen in the edematous rats

*Pea son S Stern S and McGauach T H
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REPORT OF THE COMMITTEE ON INSTRUMENTAL TECHNIQUES

DR W F HAMILTON (Chairman)
DR H D GREEN
DR ERIC OGDEN

Criteria for the auscultatory measure of arterial pressure

In the last report of the American Heart Association Blood Pressure Committee (Circulation 5 503 1951) it was suggested that the cuff pressure at which sound was first heard as the pressure within the cuff was reduced be read as the systolic arterial pressure In the appendix it was noted that the conclusion arrived at by four teams of workers after more than 100 comparisons with direct manometry is that the estimate of systolic pressure thus determined was too low by about three mm Hg This correction was not made in the committee recommendations and has not been discussed insofar as we are aware in the recent literature

The criterion suggested for the measurement of diastolic pressure however has received criticism because if for no other reason it has broken with tradition The report cited above advises that the diastolic reading be recorded at the pressure level in the cuff where all sound stops as the pressure is gradually lowered This is about 8 mm Hg below where sound muffles or fades and is found on comparison to be within a millimeter or two on the average of the true diastolic pressure It is carefully pointed out that under hemodynamic *conditions in which no cessation of sounds occurs the level of muffling should* be recorded as a questionable diastolic reading

This recommendation has been criticised as being unnecessarily complex and resulting in confusion in clinical reports in which the older (muffling) and the suggested criteria are not clearly distinguished

It seems doubtful to the committee that any serious harm will be wrought by the effort for greater accuracy indicated by the report Hemodynamic conditions (anemia hyperthyroidism aortic regurgitation) in which cessation of sound does not occur offer many other diagnostic signs than the auscultatory one On the other hand the true level of diastolic pressure in hypertension is both uniquely important and more accurately measured by the cessation rather than by the muffling of sound

Until a contradiction of data supporting this report is available and/or a theoretical basis is found for understanding the mechanism by which the Korotkoff sounds are produced it is suggested that the blood pressure pamphlet remain unrevised

Blood Pressure Norms

It was suggested that your committee concern itself with blood pressure norms and minimal hypertensive levels The competence of the committee does not extend to cover the broad statistical and clinical insight needed to cover this question adequately

Technical difficulties and ambiguities hould be in mind when comparisons are made with published or intuitively established norms Thus on new born infants agreement with directly mea ured umbilical systolic pre ure is to be had by palpation only when the arm cuff is 2 5 cm wide The conventional pediatrician s cuff gives figures 20 25 mm Hg too low Unfortunately the published figures were obtained mostly with too wide a cuff and therefore are too low

The opposite is true when cuff pressures are taken with standard arm cuffs in obese persons with large arms or in the thigh It is best to look skeptically at cuff figures obtained on people with unusually large or small arms The former are probably too high the latter too low

Ballistocardiography

This is a subject that is presently being con idered by another committee of the American Heart Association

Venous occlusion plethysmography is a technique which has been accepted intuitively because it seems reasonable The history of physiological method ology confronts us with many programs which defaulted as soon as adequate examination of methodology was made Much time has been given to getting and interpreting results by the venous occlusion method it is highly desirable that this method be compared with other directly calibrated methods

Skin temperature can be an index to blood flow only if environmental con ditions such as humidity air motion air temperature and other factors can be thoroughly known and interpreted The evaluation of the method again can come only from careful comparative experiments with a calibrated method for measuring blood flow

Errors which might stultify the re ults obtained by the injection method for measuring blood flow through the lungs and other areas or by the Fick procedure must receive careful attention in the present rapidly changing of knowledge in this field

Intravascular manometry

The u e of a catheter or other flexible connection between a pressure trans ducer and the cavity who e internal pre sure is to be mea ured is at best a make hift It is usually difficult and often impossible to place a catheter so that its intracardiac motion will not introduce pres ure changes of inertial origin which cannot be damped out without tultifying the record Getting a good intracardiac record of pre sure is a matter of good luck rather than good management with present equipment Telling a good record from a bad one is a problem that requires con iderable in ight and for which a rule of thumb is not at present available

It eems that we are awaiting the marketing of one of the everal propo ed tran ducers that can be made independent of all hydraulic columns by having its electrical parts on the end of the catheter Hazards involved in this approach among others are that the tran ducer may work loose and come off inside Whether this hazard i greater than that of having a knot form

in an ordinary catheter is questionable It may be hard to establish a stable known zero with certain models of intracardiac transducers but a recently developed model overcomes this difficulty by allowing simultaneous external registration of mean pressure through the lumen of the gauge

The agreement of investigators as to the hydrostatic level to which pressures should be referred is a goal to be sought A good case can be made for the hydrostatic level that is basic to the function or role of the pressure concerned Thus pressures in the venous system which fill the right ventricle should be considered in relation to the height of the right ventricle or the apex beat and pressures whose role is to distend and cause filtration in the capillary bed should be considered in relation to the mean height of the capillaries themselves

However the investigator refers his pressures both he and the editors of journals hould be urged to see to it that the frame of reference hould be explicitly stated so that another inve tigator may calculate his results to a comparable frame of reference Thus when venous pressures are under con sideration a figure of say 10 cm H O is quite meaningless Additional data hould be given 1) landmark for zero 2) the position of the animal or sub ject (prone supine or lateral) and 3) the dimensions of the chest

It hould al o be realized that in practically all ituations including cal culating resi tance to flow the arterio venous pressure difference is im portant *while arterial pressure alone may be meangingless In studying factors* which produce congestion and capillary filtration transmural pressure is important and may in the pre ence of appreciable ambient pressures be quite different from intraluminal pre sures The low ambient pressure in the thorax and the high ambient pressure during the contraction of the walls of the uterus or of the abdomen hould be pecified where relevant

REPORT OF COMMITTEE ON CHEMOTHERAPY IN HYPERTENSION

DR M MENDLOWITZ (Chairman)
DR J BORDLEY III DR S W HOOBLER
DR E D FREIS DR C THOMAS

The purpo e of this report is to indicate the present tatus of chemotherapy for hypertension *with the full realization that the field is* controver ial and still developing No statement as to indications for do age or value of any therapeutic agent is therefore meant to be dogmatic or final Antihyperten ive treatment with drugs is often used in a wide spectrum of hypertensive disea e The chief objective of such treatment is the prevention of subsequent structural vascular di ease with consequent organ impairment chiefly in the brain the eyes the heart or the kidneys A secondary objective is the amelioration of such symptoms as may properly be attributed to the hyperten ion especially various grades of hypertensive encephalopathy and of left ventricular failure

There is considerable agreement concerning contra indications to drug therapy but a wide divergence of opinion as to indications Uremia with severe nitrogen retention is generally considered to be a contra indication to treatment With mild nitrogen retention antihypertensive treatment may improve renal function in some cases but this should be carefully followed with daily blood urea nitrogen determinations There are exceptions to this blanket rule especially if the blood urea nitrogen be elevated on the basis of *an intercurrent reversible process such as pyelonephritis lower nephron* nephrosis or congestive heart failure Hypertension in the aged is usually considered not to be amenable to aggressive treatment although again this is true only if the hypertension is largely systolic and hence on an arteriosclerotic basis Some elderly patients in whom it can be demonstrated that the hypertension is neurogenic or with evident vascular acceleration may be treated Hypertension secondary to renal and vascular diseases such as acute and chronic glomerulonephritis amyloid contracted kidneys polycystic kidneys lupus erythematosus periarteritis nodosa diabetes mellitus Goldblatt kidney coarcta*tion of the aorta etc are ordinarily not considered amenable to antihyper*tensive treatment There are many exceptions to this rule however and each case therefore deserves evaluation *If* the hypertension is excessive therapeutic trial is justified Acute coronary occlusion or acute cerebrovascular accident are generally contraindications whereas residuals of these events are not necessarily contraindications to antihypertensive treatment Angina pectoris may be improved or made worse by treatment and each case must be evaluated separately

There is some agreement as to indications for treatment but also large areas of discord Most observers are agreed that the accelerated form or the so called *malignant phase of essential hypertension must* be treated vigorously Nearly all workers also favor vigorous treatment of hypertensive crises or encephalo*pathy especially if relatively uncomplicated by uremia There is a wide diver*gence of opinion however as to whether uncomplicated essential or primary hypertension should be treated at any age There are some who believe that since such people may be asymptomatic for many years and never develop accelerated hypertension they should not be subjected to the hazard expense and discomfort of treatment whereas others believe that all hypertension accelerates vascular disease and that early treatment is therefore important

Most workers in the field are agreed that except where treatment should be prompt and vigorous as in malignant hypertension some form of rauwolfia derivative is the drug of choice with which to begin antihypertensive treatment The results are generally better with reference to the hypertension than if a *more general sedative such as phenobarbital is used There is little difference* between the various forms of rauwolfia drug provided the dosage is standard*ized and adjusted in each case The suggested initial dose of reserpine for* example is 0 25 mg three times daily Doses greater than this are not of *additional value and increase the side actions wheras smaller doses (0 1 to* 0 25 mg once daily) often can be employed for maintenance of effect If the

rauwolfia drugs are not effective in any given case they should be withdrawn but effective reductions in blood pressure can be achieved with rauwolfia alone in many cases of hypertension. Side actions of the rauwolfia drugs consist of occasional diarrhea and nausea, nasal stuffiness, blurring of vision, fluid retention with edema, unsteady gait, a tendency toward frightening dreams, and most important, depressive psychosis. The latter reaction, which may be preceded by *agitation and insomnia, is often a late effect following four months to three years* or more of rauwolfia therapy. It is always a contraindication to continuing therapy. The other symptoms can be met by dosage adjustments and in the case of nasal obstruction by supplementation with antihistaminic drugs and vasoconstrictive nose drops. Occasionally peptic ulcer is produced or activated by rauwolfia drugs and this may be manifested by pain or by a tarry stool or hematemesis. In such cases the drug should ordinarily be discontinued. Epilepsy is considered a contraindication to rauwolfia on theoretical grounds but clinical evidence of its harmfulness is as yet incomplete.

Veratrum derivatives may be used to supplement rauwolfia on occasion but have been found by many observers not to be very useful for this purpose. If there is tachycardia and a contraindication to rauwolfia, veratrum is useful as a substitute. It has the disadvantage of the rapid development of tolerance and *of the side actions of nausea and vomiting which often appear close to the* therapeutic dose level. As a prototype, the oral dose of protoveratrine A and B is 0.4 mg spaced six hours apart with the added precaution that no food be ingested for four hours after any single dose. Dosage may be increased gradually until there is either a satisfactory reduction of blood pressure or the appearance of nausea and vomiting.

Hydralazine is a useful supplement to rauwolfia and may also be given independently. There are many side actions of the drug, including headache, nausea, vomiting, drug fever, rash and fluid retention. The most serious side action is a *lupus erythematosus like reaction with arthropathy, skin eruption,* fever and a positive L.E. cell test. This is less commonly seen if a dosage of 400 mg daily is not exceeded and rarely occurs on a dose of 200 mg daily or less. Many side actions can be avoided if the dosage begins at 10 mg three times a day and is thereafter gradually increased and if rauwolfia is administered for several weeks prior to the exhibition of hydralazine. Angina pectoris is a contraindication to the use of hydralazine and tachycardia and even angina itself may be induced by the drug in some cases.

The ganglion blocking drugs may also be used independently or in combination with other drugs. There seems to be little choice between the various preparations, mecamylamine, chlorisondamine or pentolinium. Mecamylamine has the advantage of complete absorption after oral administration but the disadvantage of prominent side effects due to parasympathetic blockade. Dosage of these drugs should begin quite low *and be gradually* increased. The initial twice daily dose of mecamylamine is 2.5 mg, of pentolinium 20 mg and of chlorisondamine 25 mg with gradual increase in amount and/or frequency until

an adequate effect is achieved or until intolerable side actions preclude further increase Coarse tremor and psychosis have been side effects of very large doses of mecamylamine given to patients already in uremia or with cerebrovascular disease

Successful use of the ganglion blocking agents requires detailed knowledge and pecial effort Dosage must be titrated to the individual requirements of each patient Some physicians prefer to use home blood pressures in the standing position for this purpose since office blood pressures are often falsely high whereas others do not favor home blood pre sures because of the anxiety they create and the inconvenience involved If office blood pressures are used it is better that they be taken by the office assistant or nur e both in the erect and in the supine positions If it is suspected that they are falsely high the attempt to reduce the erect blood pressure to completely normotensive levels need not be pressed

The complaint of dizziness or faintne s on standing relieved by recumbency is usually a good indication that dosage should be reduced regardless of the recorded office blood pressure This symptom however must ometimes be distinguished from the dizziness produced by the hypertension or by labyrinthine di ease Dosage may require adjustment because of increa ed reactivity to the drug which is induced by hot weather the ingestion of alcohol or by acute salt loss

The physician needs to be familiar with the common side effects of sympathetic blockade such as postural syncope or faintness chilling in a cold environment increased susceptibility to heat stroke and of parasympathetic blockade such as dry mouth di turbance in visual accommodation gastrointe tinal atony impotence and difficulty in emptying the urinary bladder A rare peculiar type of interstitial pneumonia has been attributed by some workers to hexamethonium whereas others believe this to be uremic pneumonitis not related to the administration of the drug Many of the e side effects do not occur with careful dosage regulation and when they do occur they are often transient Some of the side effects can be circumvented by the use of parasympathomimetic agents such as pilocarpine and neostigmine Cathartics and enemata are almost always necessary to combat the constipation often seen In fact constipation is so common that cathartics are usually given with the initiation of treatment The degree of success achieved with the ganglion blocking agents depends in large measure on the kill and patience of the physician and the intelligence and fortitude of the patient

Other drugs which are often used in the management of hypertension are the barbiturates and the tranquilizers including thorazine meprobamate and their derivatives They are useful for allaying anxiety e pecially if there is a contraindication to rauwolfia but produce little if any lowering of blood pressure *per se*

Mercurial and other diuretics are u eful upplements to the low sodium diet especially for the treatment as well as the prevention of left ventricular failure

and any of the drugs discussed in this report may be used in conjunction with the 200 mg low sodium diet provided the blood urea nitrogen concentration is checked frequently and the silent development of renal insufficiency is avoided A recent development has been the discovery that chlorothiazide a diuretic and potent saluretic agent will reduce blood pressure in hypertensive but apparently not in normotensive individuals Experience with this drug is still too limited to make definitive claims for it The drug will however potentiate the action of ganglion blocking agents One half gram on arising and at bedtime is the ordinary maintenance dose Although chlorothiazide appears to have promise the possibility of sodium chloride or potassium depletion or progressive azotemia must be kept in mind In addition enough time has not elapsed to judge the effects of this agent in the treatment of hypertension or to be certain of the absence of long term toxic effects

Hypertensive encephalopathy requires special treatment with drugs whether it occurs in pregnancy as eclampsia or in the patient with advanced hypertension There is some question in eclampsia whether such treatment increases fetal mortality Antihypertensive therapy is usually begun at once especially if the blood urea nitrogen level is below 60 Since there is often psychic obfuscation barbiturates are contraindicated Because vomiting is common drugs should ordinarily be given dissolved in five percent glucose and water solution by intravenous drip Those most commonly used for this purpose are protoveratrine and trimethaphan (Arfonad®) An alternative procedure if continuous measurement of blood pressure is impractical is to give five mg of reserpine intramuscularly When the sensorium has become clear and vomiting has stopped transition to oral treatment may be effected During drug infusion blood pressure should be brought down to no lower than 170/90 by adjusting the dose of the drug and the rate of infusion

The committee wishes to emphasize that no two cases of hypertension are alike and that therapy must be considered an individual experiment in each case Thorough clinical evaluation before treatment is mandatory especially in the severe cases It should also be remembered that the use of drugs is only one aspect of the total treatment of hypertension

REPORT OF COMMITTEE ON SURGICAL TREATMENT OF HYPERTENSION

DR EDWARD FREIS Chairman
DR WILLIAM GOLDRING
DR KEITH GRIMSON

The surgical treatment of hypertension includes procedures aimed at eradication of primary etiologic processes such as (1) unilateral renal disease circulatory ischemia or hypoplasia (2) adrenal hyperfunction due to cortical adenoma carcinoma or hyperplasia (3) pheochromocytoma and (4) coarctation of the aorta In these conditions surgical intervention is indicated providing

the patient s general condition permits and the damage has not become so far advanced as to preclude successful results of such intervention

There is marked variability of opinion concerning the value of sympathectomy in hypertension However most of the long term follow up reports in the literature suggest some prolongation of life The difficulty in a truly definitive evaluation of reports is the lack of adequate control series followed concom itantly with the treated series Comparison of surgical results with various series treated medically by other individuals in different locations and at other times always is open to some question

The ability to select favorable from unfavorable re ponders prior to surgery is the main problem Sympathectomy probably is be t indicated for patients under the age of fifty to fifty five who exhibit evidence of acceleration but without marked renal impairment (phenol sulphenphthalein excretion greater than fifteen percent in fifteen minutes and no azotemia) The operation definitely is not indicated for patients with nitrogen retention They have not tolerated surgery well and those who survive the postoperative period rarely have shown evidence of retrogression of their di ea e Patients with a slowly progressive hypertension could have sympathectomy as an elective procedure

It is the prevailing opinion that an adequate trial of anti hypertensive drug therapy including the use of ganglionic blocking agents hould be undertaken prior to advising surgery However if the trial is unsuccessful in controlling blood pres ure levels or in arresting the progress of the di ea e as hown by failure of clearing of hemorrhages exudates or papilledema in the optic fundi episodes of hypertensive encephalopathy or increasing cardiomegaly and albuminuria sympathectomy may be recommended Some authorities believe that if a patient does not respond to blocking agents he also will not re pond to sympathectomy Others believe that this is not always the ca e and also that there are patients who do not cooperate well enough for a long term medical program to be effective

The mo t practical type and extent of sympathectomy will vary with the training and experience of the surgeon and the everity of the di ea e Splanchnicectomy includes removal of the lower thoracic and the upper or all lumbar ganglia with the planchnic nerves and with or without removal of the celiac ganglia Total sympathectomy includes this and al o removal of the stellate and upper thoracic ganglia to denervate the cardiopulmonary area and the upper body This produces slowing of the heart rate Vasocon trictor path ways through the econd and third lumbar ganglia usually are not removed The purpose is to avoid incapacitating postural hypoten ion As determined by sweat and kin resistance tests ome return of ympathetic nervous activity occurs a year or more after operation Removal of intermediate ganglia uch as the iliac and the tellate minimizes functional regeneration

In general the more extensive the ympathectomy the more likely it is that there will be a la ting and significant reduction in blood pre ure However the length of the period of po toperative di ability and the occurrence of

complications of surgery also may be increased in proportion to the extent of sympathectomy This increased risk and disability may be justified in rapidly advancing or in chronic and intractable cases

Total adrenalectomy for hypertension has not been sufficiently well evaluated to warrant use other than as an experimental procedure It has not yet been proved that survival is any greater The same may be said for the combined procedures of sympathectomy and total or partial adrenalectomy The evidence available indicates that these procedures also have been unsuccessful in the presence of marked renal impairment

The principal disadvantage of sympathectomy is the inability to select with any assurance the patients who will achieve long term reduction of blood *pressure However postural hypotension and relief of symptoms is more* frequent than reduction of supine pressure Since the advent of more effective antihypertensive agents the numbr of sympathectomies done in most medical centers has decreased markedly One advantage of the surgical approach however is that it does not require meticulous and indefinitely protracted medical management such as is required with either dietotherapy or treatment with most antihypertensive agents Whatever lasting protection is achieved by sympathectomy is not entirely dependent on the patient s will to cooperate the protection obtained with a medical regimen lasts only as long as the patient desires to continue his treatment There is also some evidence to suggest that after sympathectomy the patient s blood pressure may become more re ponsive to the various forms of medical treatment

A few authorities do not believe that mere reduction of blood pressure either by sympathectomy or by the use of antihypertensive drugs has been proved to be of any real value either in preventing complications or prolonging life *Since long term tatistically definitive controlled studies are lacking it is im* possible to settle this issue one way or the other Nevertheless the majority opinion of this council is that hypertension accelerates vascular changes and that as a rule reduction of blood pressure promotes increased longevity Thus if a patient is a candidate for sympathectomy if he fails to respond to antihypertensive drug therapy or will not tolerate a long term medical regimen and if he is willing to accept surgery for its po sible benefit sym pathectomy may be advised

REPORT OF COMMITTEE ON EPIDEMIOLOGY OF HYPERTENSION

DR KENNETH KOHLSTAEDT, Chairman

DR ARTHUR FISHBERG — *DR LEVIN WATERS*

DR ARTHUR MERRILL — DR EDWARD WEISS

The application *of epidemiological methods to the study of hypertension* offers an opportunity to obtain information that will be u eful in establi hing the cause of primary diastolic hypertension and thereby aid in eliminating this

di order Studies hould not be undertaken without guidance of persons trained in epidemiology

In considering areas for future inve tigation this committee propo es that the factors be divided into three categories on the basis of need for information and practicability of study

1 In the fir t group are a number of problems which in our opinion have already received adequate con ideration and concerning which it is doubtful that additional tudies would be of value

Race—It is well known that hypertension is frequent and often severe in the Negro It is difficult to separate race from heredity and environment in the course of an epidemiological study It is likely that in the future racial back ground will become less important

Obesity—In the past being overweight has been considered a cause *per se* of high blood pressure The committee wishes to point out that errors in measuring arterial pressure by the auscultatory method on the very large upper arm of obese persons may have been responsible for the establishment of this concept The reduction in blood pressure attributed to lo s of weight may actually have been due to improved accuracy in recording pressure when the circumference of the arm was decreased The fal e correlation of obesity and hypetension can be eliminated by wrapping the cuff of the sphygmomanometer around the forearm and estimating the y tolic pre sure by palpating pulsation of the radial artery as pressure within the cuff is decrea ed

Body build and height and use of alcohol or tobacco—In the opinion of the committee there is sufficient evidence to justify the conclusion that none of these are concerned in the genesis of primary diastolic hypertension

Food—At the present time there is no evidence that food it elf is a factor in elevated arterial pres ure There is no basis in fact for the once popular belief that red meat was harmful to persons with hypertension

Physical exercise—Moderate physical exerci e is not considered harmful for patients with primary diastolic hypertension The committee does not be lieve that investigation of physical activity de erves further consideration in an epidemiological study

2 The econd category is compo ed of factors that may be important but which hould be difficult to study

The effect of age—Although evidence has hown that there is a difference between blood pres ure in children and in adults and that there is a tendency for arterial pre ure (e pecially systolic pressure) to increa e a the individual grows older a tudy of age in relation to the development of primary dia tolic hyperten ion would require numerous longitudinal tudies (observations ex tending over a prolonged period) This form of investigation is very co tly The committee believes that ob ervations made by Hamilton Pickering Rob erts and Sowry (Clin Sc *13* 37 1954) indicate the problems to be expected in obtaining information regarding the relation hip between age and blood pre ure The data presented by the e investigators do not warrant the con

clusion that primary diastolic hypertension may be a phenomenon of aging rather than of disease The relationship between age and blood pressure is admittedly a very complex problem that would be difficult to study by epidemiological methods

The role of emotional stress—A personality pattern characteristic of primary diastolic hypertension has not been defined There is insufficient evidence to support the concept that emotional stress causes hypertension A study of the role of emotions in the elevation of blood pressure would be a formidable undertaking Normotensive controls would be needed Adequate tests for emotional factors are not known and even if they were it is doubtful if a sufficient number of trained persons would be available to conduct them

3 In a third category the committee considered the factors that are believed to be important in the genesis of hypertension and that should receive priority

Heredity and environment deserve the immediate attention of investigators The measurement of blood pressure in relatives of patients with primary diastolic hypertension can be done without great expense and if properly executed a great deal of useful information could be obtained in a short time Another worth while study would be the recording of blood pressure in a large number of twins Measurement of blood pressure in large populations also might shed light on the relation of sex to the pathogenesis of hypertension

A study of environmental factors would be more difficult than problems related to heredity An epidemiological investigation if carefully controlled could be of great value in elucidating the effect of environment on the occurrence of hypertension At this time the role of sodium as an environmental factor in the genesis of primary diastolic hypertension is of paramount importance Although epidemiological studies of the dietary habits of a population are difficult a thorough investigation of the relation of both the sodium and potassium content of food and water to the incidence of high blood pressure and vascular damage would provide a great deal of useful information

It is the opinion of the committee that the evaluation of tests for hyperreactivity of the vasomotor system could be the subject of study There are no satisfactory ones available at the present time The committee hopes investigators will give attention to this problem

Time did not permit a full discussion and review of this report at the November 1957 meeting of the Medical Advisory Council It is hoped the epidemiology of hypertension may receive further consideration at future meeting

The committee wishes to thank Dr John W Ferrer Associate Medical Director of the American Heart Association for his help in providing information

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COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH
AMERICAN HEART ASSOCIATION NOVEMBER 1957

SURGERY FOR HYPERTENSION AND RELATED CARDIOVASCULAR DISEASES

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The earliest form of surgery for high blood pressure was a limited sympathectomy — splanchnicectomy The sympathetic nerves activate or regulate the blood vessels and blood flow throughout the body The splanchnic branches in particular supply the abdominal viscera Splanchnicectomy had been first theoretically considered by French physicians It had then been performed in this country by Adson Peet and other surgeons between 1930 and 1935 Surgical research on high blood pressure and interest in the sympathetic nervous system was in part a logical outgrowth of studies on low blood pressure or shock stimulated by the high mortality rate among the wounded between 1914 and 1918 Cardiovascular discoveries and their application to clinical problem have continued steadily until now cardiovascular surgery is almost a pecialty

In general there are two types of surgical approach to hypertension One is the removal of nerves organs or glands whose normal function is detrimental to a hypertensive patient The other attempts repair or replacement of diseased or worn out structures of the body All operations are based upon knowledge of structure and function of the body and of the mechanisms causing high blood pressure

The cause of hypertension is differently emphasized by the followers of two classical schools of thought One began here in Cleveland in 1933 when Dr Harry Goldblatt demonstrated that partial obstruction of the arteries to the kidneys caused hypertension in dogs Dr Irvine Page carried on some experiments to demonstrate that the culprit was angiotonin a substance released into the blood stream by the obstructed kidney Surgically this concept has led through various research steps to clinical application in the occasional cure of hypertension by the removal of one diseased kidney Within the last two years several groups have used x rays of the arteries to the kidney to demonstrate small points of obstruction and have repaired the defect or have removed one kidney Results are not always encouraging Why not remove both kidneys for patients with renal hypertension? First the patient would not live long Second Dr Arthur Grollman and others have shown that an insufficiency of kidney tissue can also cause high blood pressure the so called renoprival hypertension This in a sense is the opposite of the Goldblatt theory Similar difficult problems have to be faced in experimental and clinical attempts to bring a new blood supply to a kidney Interruption of the nerves to the kidney has not helped Research is continuing but as yet there is no reliable surgery on the kidneys for most patients with this form of high blood pressure

The second classical school of thought centers around the work of Professor C Heymans and his proof that hypertension could be caused in dogs by dividing the nerves from certain pressure sensitive areas of the arteries of the neck and heart These normally act as governors to keep blood pressure down to normal levels in anger frustration etc In patients with this common form of hypertension the buffering mechanism still functions although reset at a higher pressure level We do not yet know how to readjust the pressure setting However removal of *all* of the sympathetic nerves in animals with this neurogenic hypertension restores blood pressure to normal by disconnecting the nerve wiring circuit at its most accessible point Is it necessary to disconnect the sympathetic nervous system completely? Many experiments indicate that it is Half a sympathectomy does little in animals The sympathetic nerves to the head and heart are just as important in the maintenance of neurogenic hypertension as are those to the kidneys and abdominal viscera The operations of Adson and Peet and their subsequent modification by Smithwick in 1939 were splanchnicectomies focused on the kidneys and abdominal viscera only These operations effect some relief of symptoms and an occasional definite reduction of blood pressure Many surgeons now employ modifications of the original procedure but still limit their operation to a splanchnicectomy

Because of training with Heymans experiments in animals and a belief that neurogenic components of the hypertensive disease process are important *initiating and perpetuating factors* I started total sympathectomy in 1940 This operation includes denervation of the upper body and thoracic viscera as well as the splanchnic area Results among 220 patients so treated have been encouraging with maintained reduction of blood pressure to about normal in a third reduction but not to normal in a third and relief of symptoms and apparent increased life expectancy for most These results added to those from the use of new drugs which suppress the sympathetic ganglia demonstrate the significance of the neurogenic component of hypertension Even the present popularity of the so-called tranquilizing drugs is evidence of this There seems to be no doubt that suppression of the sympathetic nerves by drugs or surgery is at present the most practical way of benefiting patients with hypertension

Removal of the adrenal glands is another form of surgery directed at reducing blood pressure by interfering with structures which have apparently normal function Patients with loss of these glands by disease suffer from low blood pressure and may require Cortisone to keep them alive Experimentally and clinically it is difficult to produce a compromise or balance between the evils of high and those of low blood pressure If the adrenal are totally removed and then adequate doses of Cortisone are given hypertension return For this and other reasons total adrenalectomy has not become popular Research in this field continues For the present the accepted form of adrenalectomy is the removal of a rare tumor a pheochromocy

toma which secretes adrenalin and does cause a hypertension that can be corrected For the last five years Dr Harold Zintel and his associates have felt it necessary to remove *part* of the adrenal glands to reinforce the effects of splanchnicectomy Removal of ninety five percent of the adrenals may be too much for one patient not enough for the next This leaves most patients in constant need of medical supervision and Cortisone This operation has met with limited trial and popularity Sympathectomy renal surgery and adrenalectomy have been the main surgical approaches to hypertension by altering normal function

Repair or replacement of body structures is usually directed toward a main complication of hypertension hardening of the arteries or arterio clerosis *Common causes of death from high blood pressure are damage to the brain* heart and kidneys by coexisting arterio clerosis which is accelerated by the high pressure Today the recognition of the importance of low fat diet and of the use of sitosterols such as Cytellin in the prevention and management of arteriosclerosis probably will improve results of all forms of treatment of hypertension and will minimize these complications

The arteries to the brain can be damaged by arteriosclerotic obstruction of the flow of blood (minor strokes) by sudden occlusion from a blood clot (thrombosis) or by rupture and hemorrhage Dr Champ Lyons and others have demonstrated small segments of occlusion of the carotid arteries in the neck and have removed the e segments replacing them by cloth tubes or by arteries from an artery bank Also the obstructions can be cleared out from within the artery — thrombo endarterectomy This benefits patients having repeated small trokes Patients losing consciousness with the sudden development of a thrombosis within the skull have been given injections of novocain into the upper sympathetic ganglia to try to reduce spasm of collateral ves els and improve circulation This minor operative procedure may have helped some patients However there is evidence that the blood vessels of the brain enclo ed as they are in a hard skull have little sympathetic control Probably one of the mo t important relatively new developments has been the u e of cerebral angiograms to demon trate by x ray the presence of small aneurysms or ruptured vessels in patients who have had a cerebral hemorrhage and are about to have another Neuro urgeons can operate in the neck ap plying a clamp to decrease pres ure and then operate within the kull to remove clip or tie off these aneurysms

The coronary arteries to the heart can also gradually occlude or suddenly thrombo e causing di ability or death to our hypertensive patients Mo t of the re earch and the clinical advances in cardiac urgery today have been in the field of *congenital abnormalities in children and in treatment of val vular* di eases usually rheumatic in origin The techniques for heart lung pump for topping and starting hearts and for operating upon open blood less heart chambers are available for the management of coronary disea e However there is an as ociated mortality ri k even in young patients with

out coronary dısease and to the best of my knowl dge thıs type of cardıac surgery has not been applıed to the greater rısk patıent — the older man wıth coronary ınsuffıcıency and angına

Early urgıcal efforts wıth coronary dısea e both experımental and clınıcal consısted of ıntroducıng ırrıtatıng substances to cause ınflammatory reactıons ın the sac or pace about the heart which ıs called the perıcardıum Al o trıed were the attachment of lung abdomınal omental fat or other structures to the heart In the early stages of healıng ınflammatory tı ue at the sıte of a foreıgn substance ıs vascular Later ıt tends to become relatıvely a va cular car tı sue Dr Claude Beck ın Cleveland has long worked wıth the blood flow through the coronary sınus and has devısed several operatıon desıgned to develop ıntercoronary communıcatıons to ıncrease blood flow Hıs latest operatıon ıs a sımplıfıcatıon of the earlıer ones desıgned to reduce mortalıty rısk He abrades the walls of the heart and ıts perıcardıal sac ın stalls powdered asbestos and partıally lıgates the coronary sınus Thıs pro cedure has been tested both ın anımals and ın man Another operatıon de veloped several years ago by Dr Arthur Vıneberg of Montreal ıs the movıng of the ınternal mammary artery from ıts locatıon beneath the brea t bone or sternum ınto a tunnel ın the wall of the heart Experıments ındıcate that new arterıes can branch out from thıs tran planted ves el A dırect approach to clean out or replace obstructed segments of coronary arterıes was reported from Mınneapolıs by Doctors Absolan Au t Varco and Lılleheı ın 1956 Early thıs year Dr Charles Baıley of Phıladelphıa reported removal of the thıckened lınıng of a coronary artery ın two patıents He used a pecıal ınstrument to scrape or ream out the depo ıts whıch clog ıt These operatıon requıre a general anesthetıc and surgery on the surface of the beatıng heart A procedure whıch does not was developed by Dr Robert Glover of Phıladelphıa wıthın the last few years Thıs ıs the lıgatıon of the ınternal mammary artery The artery ıs easıly acce sıble for lıgatıon Becau e of ıts ımplıcıty thı operatıon has been employed frequently but there ıs extensıve debate about ratıonale and results

Experımentally a great deal of work ıs progressıng along all of these lınes Why ıs ıt then that I can a k for a show of hands by physıcıans ın thı room and probably fınd an overwhelmıng majorıty who do not advı e any surgery for the great majorıty of coronary patıents?

There are several medıcal reasons but the mo t ımportant seems to be that ıt ıs hard to know whether there ıs any ımprovement after urgery or at lea t uffıcıent ımprovement to warrant the operatıve rı k Perhaps nınety percent of good rı k patıent survıve theır ınıtıal myocardıal ınfarctıon Wıth ımproved methods of medıcal treatment more than one half of the ur vıvors lıve longer than fıve years and one thırd ten year Many patıent lıve to beyond the ten years and would be consıdered a good re ult had they had an operatıon Surgıcal patıent are neces arıly elected and therefore

constitute a omewhat different population from tho e receiving medical management I can only say that a popular operation for coronary insufficiency has not yet evolved and that generally accepted proof of the value of this surgery has not yet been presented However I can as ure you that this is a problem which is receiving extensive investigation and increasing clinical trial

My medical colleagues here are probably wondering whether I have over looked the role of surgery of the autonomic nervous sy tem in the treatment of patients with coronary insufficiency The subconscious vegetative or autonomic nervous sy tem has two main divisions One is the sympathetic The other is the parasympathetic with its vagus nerves to the heart The vagus *nerves slow the rate of the heart The sympathetic nerves accelerate the heart* and also conduct pain ensations from the heart All of my sympathectomized hyperten ive patients have a slow heart rate and should experience no coronary pain It has been reassuring to ob erve that these completely sympathectomized patients who without surgery should have had a high rate of coronary difficulty and angina have instead a low incidence of cardiac trouble I wi h I could persuade more of my surgical colleagues to include this cardiac denervation with their splanchnicectomies for hypertension

It is today a generally accepted theory that occasional patients disabled by evere angina can be relieved by ympathetic denervation of the heart Several urgeons have removed both the vagus and sympathetic to the heart as the e nerves join in the cardiac nerve plexus Here again the balance between ri k and benefit is difficult to e tabli h

The large t artery of the body the aorta and its largest branches can ob truct or dilate and form aneurysms in patients with hypertension as well as arterio clero i Successful replacements and clean out procedures have been devi ed and are commonly applied Greater difficulty is encountered in the main arteries to the legs and arms but percentages of success are encouraging The maller arteries of the body such as the coronary arterie are eldom uccessfully treated by direct arterial surgery Generally as the ize of blocked arteries decrea es from the aorta out through its branches to the extremities a regional sympathectomy becomes the operation of choice

Replacement of organs is a difficult problem I know of no one who has suggested replacing the brain Some Rus ian cienti ts po tulated and tried in animals replacement of the heart Sub titution of a kidney is more logical and American The artifical kidneys developed by Dr Willem Kolff and Dr Jack Leonard of Cleveland Dr John Merrill in Bo ton and others have proved a practical method for upporting patient with temporary renal failure Until two years ago the transplantation of *the human kidney from a* healthy individual or body to a patient has met with failure or only temporary urvival ju t as happens in dog Two years ago Dr Joseph Murray and Dr Hartwell Harri on of Bo ton succe sfully tran planted a normal kidney from a normal identical twin to his brother who was dying becau e of

lo s of function of his kidney This achievement has again stimulated re earch directed toward the immunological and other aspects of ti sue transplantation in an effort to make this feat po ible for patients who are not identical twin The barrier which has prevented successful organ transplants from one per on to another now is cracked and weakened although still trong

THE WAY TO A MAN S HEART

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A few years ago a wealthy banker approached me and said I have read all the scientific and medical literature and am convinced it is possible for you to keep me alive until I am 110 year old His financial offer for such a program was most tempting but I turned him down He presents what is today a growing epidemic of fear and anxiety There are few who choo e to remember that life is fatal and that the only really successful way to prevent old age is to commit suicide when one is young

There is considerable talk about nutrition and vitamins and how they produce bigger and better babie healthier children bigger hoes and taller basket ball players On reaching adult life in contradi tinction one is advised to do without wine women and song in order to stay alive and avoid heart disease When you go to a urgeon to have a gall bladder or other spare part removed the good doctor thinks about a lot of things He a ks himself whether an operation will relieve symptoms and whether it will cure the trouble What are the ri ks? How much will the patient be disabled? Are there other ways of olving the problem? Is the patient willing to go through an operative procedure? Will he cooperate? What are the psychological consequences? The same can be true of diets if carried to extremes they too can induce restrictions and alter the way of life be expensive and produce all sorts of emotional adju tments In fact similar to drugs or surgery they can cause harm through nutritional deficiencies and in other ways

The title of this talk i The Way to a Man s Heart I do not know whether a young lady is taught how to cook these days but that supposedly used to be the way she got her man If he cooks too well it is aid that she will get her man s in urance Cupid s arrow becomes transformed to the barbed arrow of diet delivering its ting through too much salt too many calories or too much fat The e are the ingredients which have received much attention in the fields of hypertension and athero clerosis

I should like to confuse you briefly and air a few representative examples of medical knowledge and lack of knowledge Thi will not be a complete story but ju t a few tales about salt ob e ity and fat As ome of you heard this morning there is con iderable evidence that if we reduce the amount of salt in our diet deleterious effect of high blood pressure may be lessened Lowered alt intake may lower the pre ure level a little in ome patient

relieve symptoms and help a few of the complications Diets that are very restricted may lower the amount of cholesterol in the body But now let us ask ourselves a few questions It is not established that taking away the salt in the diet cures the patient In fact it is rather hard to convince ourselves that the life of the patient is lengthened to any material extent There is little knowledge yet of the mechanisms by which low salt diet exerts beneficial effects *When the level of cholesterol drops in the blood where does the cholesterol go?* There is a remote possibility that it may go into the walls of the blood vessels just the place we should like to avoid When the cholesterol decreases after a low salt diet certain other fatty substances in the circulation are increased There are many remaining questions as you can see

What about being over weight? You have heard this story before Doctors do not like their patients to be over weight No one recommends that you go upstairs carrying a lot of suitcases and if these are built in suitcases you should logically make the load less by cutting down your weight We know that certain complications of disease are more difficult to treat in patients who are over weight and that mild forms of diabetes may be cured by weight reduction A few have suggested that decreasing the weight may have some small bearing on blood pressure levels Finally there is some evidence that there is a greater amount of atherosclerosis percentage wise in people who are over weight as compared to those who are thin But once again there are *a lot of questions For example we have no convincing proof that weight* reduction will modify processes already present In our own hypertensive clinic fat patients seem to live longer than thin ones Much more study is needed

Finally what of the role of fat in the diet? There does seem to be a relationship of some sort at least on a statistical basis between groups of persons who eat a lot of fat and those who eat less Disorders associated with high cholesterol levels in the blood seem to be those giving rise to hardening and scarring of arteries — atherosclerosis Animals fed cholesterol will develop atherosclerosis in their blood vessel And there are hundreds of statistical studies ranging from Bantus to Eskimoes contrasting the incidence of atherosclerosis among different races nations and even occupational groups But what of proteins and carbohydrates? Some studies have shown that protein may not be innocuous in fact we speak of lipo protein fat molecules that hook up with protein molecules in our circulation Other studies show that *it is almost impossible to predict the individual s* future on the basis of the cholesterol level the size of fat molecule or anything else In fact if one takes a diabetic or hypertensive population few differences can be seen in average values although the range of variety is somewhat greater in those with disease And for every theory there is a counter theory For example the Bantus appear to have less heart disease but they are often thin may have liver disease and may have vitamin deficiencies Perhaps other factors than diet are responsible Eskimoes rarely live to a ripe old age one has to be careful

about making comparisons of groups of people unless they are contrasted from the standpoint of being the same age One doctor in Great Britain showed that deaths from heart disease declined a little bit before fat rationing was introduced and then rose just after the fat rationing became more strict

You are familiar with the line that one man s poison is another s meat And so I would like to raise another problem Ma s statistics are very important They give us clues Ultimately it is the individual that should concern us If there is more heart disease in the United States does it mean that an entire population is more prone or that a few of us are more susceptible? This is another unanswered question but one which may be very *important* Someday we would like to know how to distinguish the susceptible one so that he can be treated instead of an entire population Furthermore psychological disturbances increase when we impose restrictions on entire populations

A year or two ago there was a meeting about the epidemiology of heart disease and hypertension The conclusion was reached that there is more hardening of the arteries in men than in women that there is more in older folk than in younger ones and that there is an association of some sort between fat in the diet and the prevalence of coronary artery disease All other reported associations remain hypothetical

Until more knowledge is available we can only try to approach a balance The American diet is rather high in fat It makes good sense to lower its fat content by shying away from butter and cheese and the fat on the margins of roast beef

It seems to me we must retain a clear distinction between what we know and what is still a continuing experiment This is not a plea for discarding any of the gains we have made or for throwing in the sponge it is more a plea for retaining certain attitudes so that we can advance at a faster pace What we really need to do is to devise and carry out more definitive studies to find continued support for the right kind of investigation We are still at the beginning and much needs to be done to elucidate the various pathways to a man s heart

THE USEFULNESS OF DRUGS IN THE TREATMENT OF HYPERTENSION

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The treatment of any disease aims to cure or failing this to relieve its symptoms and prevent its complications If the disease is one which runs a rapid and predictable course such as an acute infection the results of treatment can be evaluated in short order in contrast it may take years of patient effort to assess the effectiveness of a given treatment of a chronic

illness such as essential hypertension with its relatively unpredictable course In those hypertensive patients whose treatment is aimed at the prevention of *symptoms and complications that have not developed* the results of preventive treatment can only be appreciated in general terms Such preventive treatment is commonly used because most physicians believe that a significant degree of sustained hypertension will eventually have sequelae in the form of strokes or heart attacks which are caused in part at least by the blood pressure

Hence while potent antihypertensive drugs have been widely used for the past seven or eight years the course of essential hypertension is so variable and usually so prolonged that many more years must pass before we can know whether these drugs are really as effective as they seem to be now Still at the present time we can assess with confidence the effectiveness of these agents if we limit the consideration to that group of patients who suffer from a rapidly advancing form of the disease so called malignant or accelerated hypertension This disease has a relatively brief and predictable course Untreated it is rapidly fatal for nearly all such patients For example in *1939* Keith Wagener and Barker summarized the clinical courses of *146* patients with malignant hypertension more than fifty percent of these were dead within six months some eighty percent had died by the end of the *first year only two percent were alive at the end of the fourth year* At that time less than twenty years ago no really effective treatment was available thus a comparison of their survival with that of patients with malignant hypertension treated by modern methods can serve as an index of what has been our recent accomplishment

The aim of treatment in hypertension is with due care to lower and maintain diastolic blood pressure at normal or nearly normal levels thus abating the symptoms and complication of the small blood vessel (arteriolar) disease characteristic of hypertension and preventing the complications of *large blood vessel disease (arteriosclerosis) which is almost always accelerated* by hypertension

When we compared our group of sixty one malignant hypertensive patients whom we had treated during a five year period with that group reported about twenty years ago by Keith Wagener and Barker we found thirty percent of our patients died during the first year of treatment as opposed to eighty percent of theirs It is important to realize that this thirty percent includes those patients who died in 1952 when we had little skill in the use of these antihypertensive drugs and little variety in their selection as well as those who died in *1955 when we had considerably more experience and* a wider selection of drugs Hence our experience in 1952 was understandably less gratifying than our more recent results At the end of five years some thirty percent of our group was still alive while the comparable datum for the untreated group was two percent

Thus modern treatment is definitely helpful in malignant hypertension this becomes more obvious when one examines the causes of death in the twenty eight patients who died during treatment Ten advanced cases died of kidney failure and even of a peculiar pneumonia that complicated one kind of treatment Five patients died of myocardial infarction four of cerebral hemorrhage and one of a ruptured aortic aneurysm The cause of death of one patient is unknown None of the patients died of heart failure which was previously an important cause of death Of those who died of kidney failure all had extensive kidney disease before treatment was started In short treatment has so changed the course of this type of hypertensive disease that patients no longer die of the effects of small blood vessel disease from these they usually recover Some do so only to die months or years later of the complications of large blood vessel disease—arteriosclerosis

There is no one drug for the treatment of malignant hypertension Any of the antihypertensive drugs may be useful as long as the diastolic blood pressure is well controlled This is the important point diastolic blood pressure must be maintained at normal levels or as near normal levels as possible if the disease is to be well treated The choice of a drug should be made according to the severity of the hypertensive disease and the response of the patient If the patient is very ill and requires rapid blood pressure control a ganglion blocking agent is usually chosen if a few more days or weeks of hypertension will not be harmful to the patient hydralazine or reserpine may be tried for although these drugs may not be so promptly effective they are not so difficult to administer In each instance the goal is the reduction of diastolic blood pressure to normal levels not often is this goal achieved but we always strive for it

Even though modern treatment of hypertension is effective many problems remain We know so little about the fundamental mechanisms of the disease that our treatments are nonspecific furthermore they are clumsy for the patient and are often associated with troublesome and sometimes dangerous side effects Because we do not understand the basic mechanisms we cannot predict the type of treatment which will be effective for a particular patient Perhaps each of the drugs will lower his blood pressure perhaps none will or perhaps a combination of drugs will be the most helpful Lastly although we have accomplished a good deal in the treatment of severe and progressive hypertensive disease we are faced with the problem of the arteriosclerosis which has been accelerated by the preexisting hypertension We are just beginning to face up to this problem seeking means for its prevention or cure We hope that it will fade in importance as treatment becomes more specific prompt and lasting as a result of learning what are the basic mechanisms of the disease in all its various forms